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Emergent intubation: tips, tricks, and evidence

Aaron M. Joffe, DO, FCCM Seattle, WA

Learning Objectives
At the end of this lecture, the reader should be able to:

1. Describe what everyone in attendance at an intubation should know regardless of the role they are playing
2. To discuss aspects of optimizing first attempt intubation success
3. To describe a risk stratification scheme for tracheal extubation

Introduction:

Emergency tracheal intubation outside of the OR is required in patients requiring immediate assistance with oxygenation. Compared to elective intubation in the OR for general anesthesia the occurrence of difficult intubation outside of the OR is several-fold higher. In addition, airway-related complications such as hypoxemia, hypotension, esophageal intubation, and aspiration are far more common as is cardiac arrest. The Fourth National Audit Project by the Royal College of Anaesthetists (NAP4) has most recently and comprehensively highlighted this. Of the 184 reported airway events, nearly 20% occurred in either the ICU or emergency department (ED) of which nearly two-thirds directly resulted in death or permanent neurologic injury. Furthermore, factors considered to be contributory or causal were often related to communication failures or the judgment and training of the operators. In over 1/3 of events in the ICU, the quality of airway management was judged to be poor.

Patient Positioning

Appropriate positioning of the patient in preparation for airway instrumentation is an important, but often neglected aspect of airway management. Over 40 years ago, Stept and Safar reported on "Rapid Induction/Intubation for Prevention of Gastric-Content Aspiration." As part of a multi-step process, practitioners are instructed by step 6 to "place patient in semisitting, V-position, with trunk elevated about 30 degrees…" Positioning patients in this manner may improve the efficacy of preoxygenation, maintain the airway in a more anatomic position, improve laryngeal exposure, and, of course, decrease the chances of passive regurgitation. This can be accomplished quite readily with most modern hospital beds by first putting the bed in trendelenburg position and pulling the patient up until their occiput rests on the edge of the mattress. Next the head of the bed is elevated to 30 degrees. And, lastly, if necessary to ensure that the external auditory meatus is aligned with the sternal notch, an additional headrest can be placed under the occiput. This position has reported to decrease complication rates in emergent out-of-operating room intubations. An extreme version of this, which has been recently reported, called "face-to-face" intubation, involves providing all airway management with the patient in a nearly fully seated position. Airway instrumentation is accomplished with a video laryngoscope.

Direct versus Indirect Laryngoscopy

The use of newer rigid video laryngoscopes to increase patient safety by increasing first attempt intubation success and/or decreasing time to successful intubation remains contentious. A recent meta-analysis evaluated a number of prospective randomized trials comparing direct laryngoscopy (DL) with the Glidescope (GS). The proportion of intubations taking place with a full view of the glottis (Cormack-Lehane grade 1) was significantly higher with the GS than DL. This was true for all intubations as a whole, although the effect was greater among intubations labeled as difficult. However, neither the first attempt success rate nor the time to intubation was different between techniques. This was due to, in large part, a small number of studies including novice or inexperienced operators, which did show the GS to be beneficial, having been balanced by a larger number of studies of expert operators where no benefit was reported. In addition, a recently published pilot prospective randomized trial of DL versus GS for intubation in the intensive care unit also failed to show a difference in any important outcome. It is also notable that while this study was small with 40 patients, it included what many would consider inexperienced operators, the very group that had been previously reported to benefit for the GS. At this time, there is little high quality data to support the widespread preferential use of a GS over DL by experienced personnel for initial intubation attempts. Two recent pragmatic trials of ICU intubations, which were largely attempted initially by junior trainees or staff also failed to show superiority of the newer technology. It should be noted that the most current version of the ASA guidelines states that "consideration of the relative clinical merits and feasibility of four basic management choices" should be made. Choice number 3 is "video-assisted laryngoscopy as an initial approach to intubation."

Extubation of the difficult airway

Extubation has traditionally been considered a routine part of the emergence from anesthesia. Anecdotally, the need to keep a patient who presented for elective non-major surgery has been considered a failure on the part of the anesthesiologist to perform their duties adequately. However, it is now recognized that some patients are at risk for extubation failure post-procedure and that failure to acknowledge this phenomena may lead to serious morbidity or death. For example, multilevel anterior cervical spine surgery with a duration > 5 hours and > 300 ml blood loss have been reported to increase the risk of upper airway obstruction post-procedure. In a retrospective review of over 2000 patients who were extubated while in the ICU of a large urban tertiary care referral hospital, nearly 1 in 5 (19%) required reintubation at some point during their hospitalization. The median time to reintubation was <24 hours with 1 in 10 of those patients needing to be reintubated within 1 hour of extubation. Additionally, the need for reintubation was associated with higher ICU length of stay, in-hospital mortality, and greater cost of care. Most recently, nighttime extubation (1900-0659 the next day) was also reported to increased mortality. On a national level, the fourth National Audit Project of the Royal College of Anaesthetists reported that more than 1 in 4 airway related events occurred at extubation or in the recovery area post procedure. The root cause of 100% of these events was judged to be due to some form of airway obstruction. Highlighting that these events are not innocuous, death or permanent brain damage occurred in 3 instances with all of the remaining patients requiring ICU level care. In response, the Difficult Airway Society of the United Kingdom has recently published extubation guidelines. As there is a dearth of literature support for any particular risk stratification or algorithm, what these types of guidelines chiefly offer is a prompt to actually consider the likelihood of extubation failure in any given patient. Underscoring the paucity of data with which to guide specific recommendations is the use of airway exchange catheters over which extubation takes place. In adults, only 430 patients contained in 3 case series have been reported, all of which were considered at high risk for extubation failure. However, extubation failure was reported to occur in only 13.4% of these patients overall (58/430) indicating that even in well selected patients, the use of the exchange catheter was unnecessary more than 85% of the time. The data for use of a SAD to bridge patients from tracheal tube to spontaneous respiration without an artificial airway is sparser still with a total of 41 patients reported to date with a 0% extubation failure rate.

Conclusion

Practitioners are likely to encounter difficulty in airway management far more often than they are accustomed to when performing these tasks outside the operating room. In addition, the incidence of serious complications is also higher. These complications are not simply a brief blip on the monitor screen, but rather are associated with a several fold risk of death or permanent disability. In order to optimize pre-oxygenation, laryngeal exposure, and to decrease the risk of gastric-content regurgitation, patients should be positioned in a 30 degree head up position. Currently, no new airway technology has been shown to be superior to direct laryngoscopy for initial attempts at instrumenting the airway among expert operators for critically ill patients overall. Of course, no airway management technology will be successful 100% of the time. Practitioners should familiarize themselves with alternative techniques. While literature estimates of extubation failure vary depending on the population studied and the time frame within which extubation was not considered to be a success, it occurs with some regularity in critically ill hospitalized patients. Additionally, perhaps one-in-ten of these events will occur in the first hour after extubation. Given that the consequences of a lost airway may be catastrophic, a well articulated reintubation plan should be developed for patients who possess high-risk features for extubation failure.

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7. CME Questions

1. All of the following are correct regarding etomidate except?
   a. Glucocorticod production may be inhibited for up to 72 hours after a single dose
   b. Hemodynamic stability is maintained better during induction of anesthesia than with other agents
   c. All-cause mortality in patients with sepsis may be negatively effected by its use
   d. None of the above

Answer: b

2. The final outcome of critical airway management can be conceptualized as being determined by the interaction of which of the following variables?
   a. Patient
   b. Personnel and equipment
   c. Time
   d. All of the above

Answer: d

3. Which of the following patients is most at risk of extubation failure?
   a. 25 year-old polytrauma with cervical spine fractures, intubated pre-hospital, in ICU. He is in a hard cervical immobilization collar and has a BMI of 41 kg/m^2. He is awake, follows commands, and has passed his spontaneous breathing trial. A cuff leak is present.

b. 45 year-old man who has undergone a 2-level lumbar decompression and posterior spinal fusion in prone position. Blood loss was minimal and the surgery was 2.5 hours in duration.

c. 65 year-old female who has had a large left middle cerebral artery territory stroke with right sided motor deficits. She requires frequent oral suctioning.

d. 75 year-old man who has undergone a carotid endarterectomy

Answer: b

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Implications of Immunological Cancer Therapies for Perioperative Care

Gregory Fischer **New York, NY**

Classic Chemotherapy, together with surgery and radiation therapy, has represented the main stay of cancer therapy for over 100 years.[1] Chemotherapy represents a general term describing pharmacological agents that are non-specific, yet toxic to all cells within an organism. Many chemotherapeutic agents are not only cytotoxic to cancer cells but also to normal cells with high mitotic rates such as hair follicles, mucosa of the GI tract and bone morrow. Consequently, hair loss, GI symptoms and myelosuppression are common side effects caused by numerous chemotherapy agents. Anesthesiologists have become aware of side effects of various chemotherapeutic agents that influence perioperative management such as doxorubicin induced cardiomyopathy[2] or pulmonary fibrosis and oxygen toxicity caused by bleomycin.[3]

As a result of the these side effects and persistently high mortalities rates in advance staged cancers interest has shifted towards alternative approaches. The human immune system has a natural ability to identify and destroy cancer cells circulating within the body. To leverage this ability would represent a revolutionary approach in fighting cancer. Unfortunately, it is in the nature of cancer cells to develop cloaking mechanisms to elude the host's immune system.

The immune system can be divided into two sub-parts. The first, or the innate immune system, is nonspecific. It is immediately available to defend the host against invasion and consists of barriers (e.g. skin, mucosa), cells (e.g. NK cells, macrophages, mast cells) and inflammatory systems (e.g. complement system). The other subsystem is the acquired immune system that is comprised of the B and T cell systems. This acquired immune response takes time to develop, but is specifically geared towards a specific antigen and additionally entails a memory function. The two parts of the immune system should not be viewed in isolation, but rather as complementary, for example the acquired immune system requires antigen presentation by the antigen presenting cells (APCs) of the innate immune system in order to start the activation process. A brief review of the human immune system will be provided during the RCL.

Therapeutic Antibodies

Cancer cells express different surface antigens, and depending upon their presence, give the cancer a specific genetic fingerprint allowing medical oncologists to target them with tailored treatment strategies. The antigen/antibody interaction can lead to death of the cancer cell by either activating apoptotic pathways within the cell, activating the complement system, making the cancer cell detectable to phagocytic cells of the immune system or by linking a toxic component to the antibody (e.g. radioactive agent).[4]

The receptor status of breast cancer cells is a classic example. Aside from the estrogen or progesterone receptors much interest has focused surrounding the presence of the human epidermal growth factor receptor-2 (HER-2). When present (~20%), Trastuzumab (Herceptin®), a monoclonal antibody can be administered to these patients. Anesthesiologists should be aware that a well-described side effect of trastuzumab therapy is cardiomyopathy, which has been reported to occur in 2.5% versus 0.4%in patients taking trastuzumab versus those who are not.[5] In contrast to cardiotoxicity from doxorubincin, trastuzumab-related cardiotoxicity does not appear to be related to cumulative dose. It is often reversible with treatment discontinuation, and rechallenge is often tolerated after recovery.

Check point Inhibitors

Each T cell is characterized by a unique T cell receptor (TCR). It is through this TCR that the T cells can examine the surface antigens of all cells in the body and differentiate them as being either "friend or foe". If a dangerous antigen is recognized (e.g. cancer cell or microorganism), then the T cell can, with the help of support mechanisms, proliferate and become a clone. This army of T cells with identical TCRs will then seek out all cells that express this antigen and destroy them. Unfortunately, as discussed above, cancer cells have the ability to cloak themselves from the host's immune system. This is accomplished by altering the expression of surface tumor antigens (the tumor cell's fingerprint) and by expressing surface proteins that induce immune cell inactivation such as cytotoxic T Lymphocyte associated antigen 4 (CTLA 4) or programmed cell death protein 1 (PD 1).[6] By inhibiting these inhibiting pathways oncologists hope to unmask the tumor cells from the immune system allowing T cells to recognize the tumor cells and destroy them. Currently there are three FDA approved drugs available, ipilimumab (Yervoy®), pembrolizumab (Keytruda®), and nivolumab (Opdivo®).

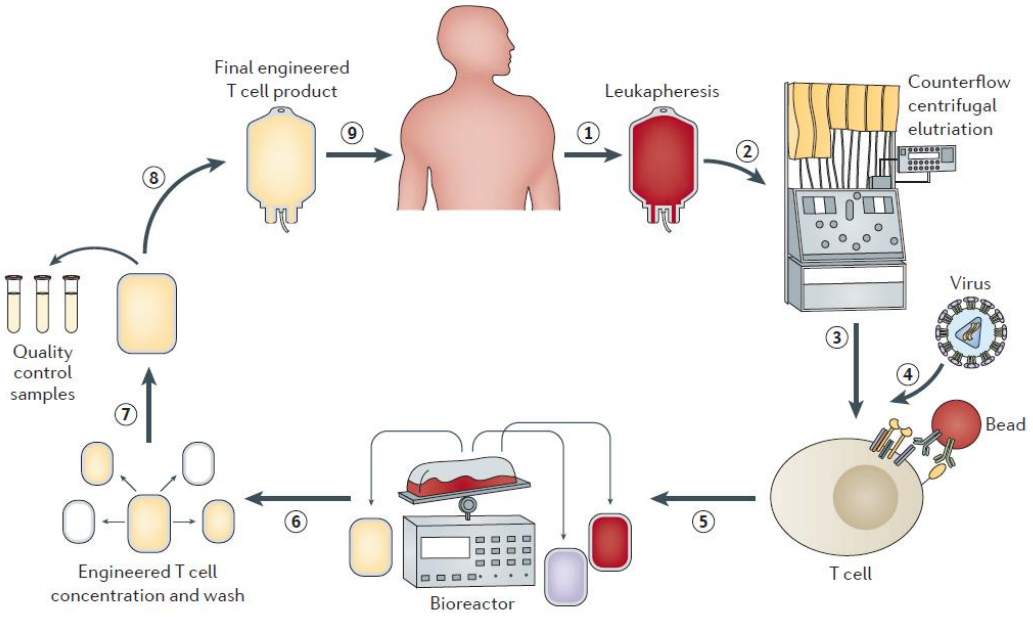
Unfortunately, as with all therapies, checkpoint inhibitor therapy comes with a price. By inhibiting the inhibitory pathways the host organism becomes susceptible to autoimmune complications. Dermatitis, hepatitis and colitis are common side effects of checkpoint inhibitor therapy. More seldom complications include pneumonitis and endocrinopathies.[7,8]

It is of interest to note that many patients do not show complete remission of their disease under check point inhibitor treatment, but develop a chronic state during which there is either some regression or at least no progression in tumor burden, thus turning cancer into a chronic disease state. Consequently, it should be expected that with ongoing advances of this treatment option that anesthesiologists will soon be taking care of patients on chronic checkpoint inhibitor therapy presenting for both oncological as well as non-oncological surgeries.

CAR-T Therapy

One of the newest and most exciting developments in the field of immunotherapy is the development of engineered T cells, also known as chimeric antigen receptor (CAR) T cell therapy.[9] As previously discussed the ability of the TCR to recognize a specific antigen builds the foundation of how the acquired immune system functions. Cancer cells have developed escape mechanisms to "hide" themselves from our immune system. CAR-T cell therapy is based on the principal that engineered T-cells can bypass these cloaking mechanisms of cancer cells by directly being able to interact with a surface antigen without the immunological checks and balances that are physiologically in place to avoid overzealous activation of our immune system.
Engineered T cells are created by harvesting the patient's own T cells via leukapheresis. The harvested cells are then sent to a laboratory specializing in the technology of engineering T cells. There, the lymphocytes are cultured and stimulated. A viral vector is utilized to alter the genetic expression of the TCR. These engineered cells are then washed and concentrated and cryopreserved. After quality testing the CAR-T cells are sent back to the facility and transfused into the patient. The process takes roughly 10 days to complete. (Image 1)

Image 1[7]



While in theory the engineered T cells can be made to recognize any antigen, to date the most successful trials have been undertaken with the engineered TCR designed to recognize the CD19 antigen, which is commonly found in hematologic malignancies.

Unfortunately, bypassing the checks and balances of the immune system does not come without a price. In a pilot study investigating the use of CD19-directed CAR-T cells a severe cytokine-release syndrome (CRS) occurred in 27% of the participants. The CRS presents as a systemic inflammatory syndrome, which in severe cases can lead to multiorgan failure and death. Treatment options consist of the administration of an anti-interleukin-6 receptor antibody (tocilizumab) or the administration of systemic steroids, which in turn destroy the CAR-T cells.
While the CRS is a feared complication the results from this preliminary trial are extremely encouraging. Complete remission was achieved in 90% of patients with an estimated six-month event-free survival of 67% and overall survival of 78%.[10] As a result FDA approval for this technology is expected to occur in the fall of 2017.

This is indeed an exciting time to be involved in the field of oncology. Thanks to better understanding of our immune system oncologists are now able to utilize its strengths to combat cancer. Unfortunately, these therapies do not come without a price. If we are to believe what many experts in the field are currently predicting, that as a direct result of these new therapies cancer might become a chronic condition, we as anesthesiologists need to inform ourselves of potential interactions and what consequences they will have on the management of our patients during the perioperative period. The goal of this RCL will be to provide the attendee with a review of the immune system, an overview of the working mechanism of these agents and then discuss potential interactions they might have on perioperative management.

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ANESTHESIOLOGY 2017
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Anesthesia for Cesarean Delivery

Paloma Toledo, MD/MPH **Chicago, IL**

Cesarean Delivery in the United States

Childbirth is the most common reason for admission to a hospital in the United States (US),[1] and cesarean deliveries are one of the most commonly performed surgeries. There has been an increase in the rate of cesarean deliveries, and this has become an issue of increasing public health concern. In a study by investigators from the Consortium on Safe Labor, data from 228,668 deliveries were weighted to represent a national sample and the overall cesarean delivery rate was 30.5%.[2] This rate has been increasing since the mid-1990s, and while the cause of this increase is multifactorial, one important contributor was a sharp decrease in the number of women who attempted a trial of labor after cesarean delivery (TOLAC).[3] Professional guidelines by the American Society of Anesthesiologists (ASA) and American College of Gynecologists state the need for "immediate availability" of anesthesia and surgical personnel, limiting the number of hospitals that provide TOLAC services. Other important contributors to the increasing cesarean delivery rate include increasing rates of obesity, multiple gestation, and advanced maternal age.[2] Projections estimate a continued increase in the cesarean delivery rate over time. Therefore, attention to the anesthetic management of these patients will continue to be of increasing importance.

Role of anesthesia in preventing of cesarean delivery

The incidence of breech presentation is approximately 3-5%, and cesarean delivery is usually recommended over vaginal delivery when the fetus is in a breech presentation.[4] External cephalic versions (ECV) are often performed in an attempt to avoid cesarean delivery. The use of neuraxial anesthesia may increase the success of external cephalic versions, and thus have a role in decreasing the overall cesarean delivery rate. A meta-analysis of all of the randomized controlled trials evaluating neuraxial compared to no anesthesia (or systemic analgesia) for external cephalic version identified a possible dose-response relationship between the density of the block and ECV success.[5] Four studies that used analgesic dosing found no difference in the success of versions, while anesthetic dosing was associated with an increased success rate.[5] The proposed mechanism for the higher success rates is possibly through improved muscle relaxation and improved maternal comfort during the procedure.[6] To date, no published study has compared anesthetic to analgesic dosing for neuraxial blocks; however, the impact of anesthetic dosing (7.5 mg intrathecal bupivacaine) compared to no anesthesia or systemic opioids is profound (87% success rate in the anesthetic group compared to 58% in the control group, P= 0.012).[7]

Anesthetic management for routine cesarean deliveries

While the specific management of any case should be decided on an individual basis, the typical sequence of events for providing anesthesia for cesarean deliveries is as follows:

1. Preoperative assessment and consent
2. Aspiration prophylaxis
3. Placement of monitors
4. Administration of antibiotics
5. Patient positioning
6. Anesthetic options for surgical anesthesia
7. Fluid co-loading
8. Management of hypotension
9. Administration of uterotonics
10. Postoperative analgesia planning

1. *Preoperative assessment:*

A thorough preoperative assessment should be performed for all cases. The Practice Guidelines for Obstetrical Anesthesia from the ASA state that specific attention should be given to relevant obstetric issues that may complicate the surgery (e.g., obesity, hypertensive disorders of pregnancy, and number of previous cesarean deliveries).[8] Physical examination should include an examination of the back if neuraxial anesthesia is planned.[8] If the patient has been laboring, or a significant interval of time has elapsed since the original preoperative evaluation, reassessment of the airway should be performed, as studies have shown that there may be changes in the class of the airway as pregnancy/labor progresses.[9] The decision to obtain routine laboratory analysis prior to a cesarean

delivery remains controversial. Routine laboratory analysis is not necessary for all patients; however, in high-risk patients, such as those patients who have symptoms or medical conditions that may be consistent with coagulation disorders, a platelet count and/or coagulation studies should be obtained.

A sample of the patient's blood should be sent to the blood bank for all cesarean deliveries. The decision to type and screen or type and cross match blood should be made based on the likelihood of requiring a blood transfusion.

Consent:
Patients should be informed of the risks and benefits of the anesthetic planned for the procedure. While there are no specific guidelines as to what information needs to be communicated, generally the most common risks should be discussed. For neuraxial anesthesia these should include infection, bleeding, risk of postdural puncture headache, hypotension, and patchy/failed block requiring conversion to general anesthesia.

2. *Aspiration prophylaxis:*
The American Society of Anesthesiologists recommends withholding clear liquids for 2 hours prior to elective cesarean deliveries and withholding solids for 6-8 hours, depending on the fat content of the meal.[8] Controversy has recently arisen around whether laboring women should be allowed to eat light meals during labor. A Cochrane review evaluating oral intake in labor found no difference in labor or neonatal outcomes when low-risk patients were allowed liquid/solid intake,[10] and concluded that low-risk patients should be allowed to eat/drink, yet none of the studies included in the meta-analysis were powered to assess maternal aspiration as a primary outcome. The ASA Practice Guidelines for Obstetrical Anesthesia state that solid foods should be avoided during labor.[11]

Prior to cesarean delivery, pharmacologic aspiration prophylaxis should be given. Three classes of drugs are routinely used: non-particulate antacids, H_2-receptor antagonists, and dopamine antagonists. Of the three, in an emergency cesarean delivery, the most important to administer is the non-particulate antacid as it has the fastest onset and decreases gastric acidity.

3. *Monitors:*
As for all surgical procedures, ASA standard monitors are required. Invasive hemodynamic monitoring is not required for routine cesarean deliveries, but should be considered on a case-by-case basis for high-risk deliveries or patients with cardiopulmonary disease. The American College of Obstetrics and Gynecology states that fetal heart rate should be documented prior to surgery.

4. *Antibiotics:*
The American College of Obstetrics and Gynecology recommends that antibiotic prophylaxis be administered within 60 minutes of the start of a cesarean delivery.[12] Antibiotic administration should not be delayed until after umbilical cord clamping as several randomized controlled trials have demonstrated that there is a decrease in endometritis and/or wound infection when antibiotics are administered prior to incision, as opposed to umbilical cord clamping, with no increased adverse events for the mother or the fetus. In the event of an emergency cesarean delivery, antibiotics should be administered as soon as they are available.

5. *Patient positioning:*
Left uterine displacement (a minimum of 15-degree leftward tilt) should be utilized to prevent aorto-caval compression syndrome. After delivery of the infant, the left tilt may be removed.

6. *Anesthetic options for surgical anesthesia:*
Neuraxial anesthesia (spinal, epidural, or combined spinal-epidural anesthesia) remains the most common type of anesthesia used for cesarean delivery.[13] Alternatives to neuraxial anesthesia include general anesthesia and local-infiltration anesthesia. The type of anesthesia selected for cesarean deliveries needs to be tailored to the patient situation. To a certain extent, the anesthetic plan is determined by the urgency of the cesarean delivery.

Neuraxial anesthesia:
The majority of cesarean deliveries are performed using neuraxial anesthesia, with the most common anesthetic being a single-shot spinal. A T4-T6 dermatomal level should be established prior to commencement of the surgery, otherwise the patient may experience breakthrough pain and require supplemental opioids, or conversion to general

anesthesia. The assessment of sensory level should be to touch/pinprick as the discrepancy between cold and touch may exceed two dermatomes.[14]

Common regimens for spinal anesthesia include a local anesthetic agent with a short acting opioid. The addition of the opioid allows for a reduction in the local anesthetic dose, thus decreasing the incidence of hypotension and other local anesthetic-related side effects. For patients without clinical contraindications, morphine is often added for postoperative analgesia. In patients in whom the duration of surgery is anticipated to exceed the duration of the spinal, epinephrine may be added to the spinal, or alternatively, an epidural or combined spinal-epidural technique may be chosen.

Epidural anesthesia may be chosen for the initiation of anesthesia (de-novo placement), or used in laboring women with an in-dwelling epidural catheter.

Choice of local anesthetic in patients with in-dwelling labor epidural catheters:
The clinical situation will influence the decision for what local anesthetic is used. In emergency cesarean deliveries, (those in which there is an immediate threat to the life of the mother or fetus), 3% chloroprocaine is the most expeditious choice.[15] In the absence of fetal compromise, or when there is fetal compromise that responds to therapy, a slower-onset local anesthetic such as 2% lidocaine may be chosen. The advantage of lidocaine over chloroprocaine is that it appears that chloroprocaine interferes with the efficacy of epidural morphine.[16] The mechanism of this interaction is not completely understood.

General anesthesia
General anesthesia is required in emergency situations where there is insufficient time for placement of neuraxial anesthesia, or when patients have contraindications to neuraxial anesthesia. A rapid sequence intubation is indicated for parturients undergoing cesarean delivery, as all patients undergoing general anesthesia are considered full stomachs. General anesthesia is associated with a shorter decision-to-incision interval when compared to neuraxial anesthesia. The trade-off is increased neonatal depression, lower Apgar scores, and an increased likelihood of postpartum hemorrhage.[17]

The following is a common approach to general anesthesia.[18] Induction and intubation should occur after surgical site antisepsis and confirmation that the surgical team is prepared to proceed with surgery. The patient should initially be ventilated with 100% oxygen and 1 MAC of a potent inhalational agent. Following delivery of the infant, nitrous oxide may be added, and the concentration of volatile agent should be reduced in order to mitigate the effect of the volatile agent on uterine tone. Benzodiazepines and opioids may now also be administered. As the risk of hemorrhage is increased with general anesthesia,[19] the dose of oxytocin administered after delivery should be increased.[20,21] Other actions should include decompression of the stomach with an orogastric tube and temperature monitoring. Patients should be extubated awake and monitored in the post-anesthetic recovery unit.[22]

Local-only anesthesia:
In situations where anesthesiologists are not readily available, a cesarean delivery may be preformed under local anesthesia. Lidocaine (0.5%) is used to sequentially anesthetize the skin, subcutaneous tissues, fascia, and peritoneum. The obstetrician should make a vertical abdominal incision and not exteriorize the uterus.

7. *Fluid co-loading:*
Hypotension is the most common complication of spinal anesthesia following cesarean delivery.[23] Side effects of hypotension could include nausea/vomiting, loss of consciousness, maternal cardiac arrest, and decreased uteroplacental perfusion resulting in neonatal acidosis. Current evidence suggests that crystalloid preloads are ineffective at preventing hypotension and instead co-loading should be performed to reduce hypotension and vasopressor requirements.[24] Colloids may possibly be more effective than crystalloids when given as a co-load;[25] however consideration to the side effects of colloid should be given (pruritus, coagulation abnormalities, and severe allergic reactions).

8. *Management of hypotension:*
Phenylephrine and ephedrine are the two most commonly used vasopressors for treatment of hypotension in cesarean deliveries. Higher doses of vasopressors are required for treatment of hypotension in pregnant women

compared to non-pregnant women due to the physiologic dependence on the sympathetic nervous system and down-regulation of adrenergic receptors.

Phenylephrine is the preferred vasopressor in obstetrics as ephedrine crosses the placenta which results in in fetal tachycardia and possible neonatal acidosis.[26] The ED_{90} for bolus administration phenylephrine following spinal anesthesia has been shown to be 150 mcg (95% CI: 98-222 mcg).[27] A suggested starting dose for ephedrine would be 10 mg. Current evidence does not support the use of a fixed-rate phenylephrine infusion;[28] however, if an infusion is to be used, clinicians should start with lower doses (25-50 mcg/min), as these doses are associated with less reactive hypertension.

9. *Administration of uterotonic agents:*
Oxytocin is considered the first-line agent for prevention of postpartum hemorrhage following cesarean delivery. The optimal dose and route of delivery are not established. Recent evidence suggests that adequate uterine tone can be achieved with bolus doses as low as 0.5-3 IU.[20] Bolus administration of oxytocin has been associated with many undesirable cardiovascular side effects, such as hypotension, tachycardia, and electrocardiogram changes that may be suggestive of myocardial ischemia.[29] Many institutions have therefore transitioned to the use of oxytocin infusions following umbilical cord clamping at cesarean delivery. The ED_{90} for oxytocin delivered as an infusion has been estimated to be 0.4 IU/min using an up-down sequential allocation with a biased-coin design.[21] There does not appear to be a benefit from administration of a bolus of oxytocin prior to initiation of an oxytocin infusion.[30] Higher doses of oxytocin may be necessary after prolonged labor with oxytocin induction/augmentation, as animal evidence suggests that there is receptor desensitization with increasing doses of oxytocin.[31]Although transient hypotension is common after the bolus administration of oxytocin, EKG changes, particularly ST-segment depression, are concerning side effects.[32] While the electrocardiogram changes are likely not reflective of myocardial ischemia,[32] it is prudent to use the lowest effective dose of oxytocin in order to avoid possible iatrogenic injury.

Postpartum hemorrhage is one of the leading causes of maternal mortality worldwide. Mortality from hemorrhage in part is due to difficulty recognizing the amount of blood lost,[33] and delay in initiating treatment for the hemorrhage. In the setting of postpartum hemorrhage due to atony, additional uterotonic agents may be necessary. In addition to oxytocin, the two most commonly used classes of agents are ergot alkaloids and 15-methyl prostaglandin $F_{2\alpha}$.

10. *Postoperative analgesia management:*
There are two components to postoperative pain, the somatic (incisional) and visceral (uterine) pain. Options for postoperative analgesia are described below.

Neuraxial opioids:
Neuraxial morphine is the gold standard for achieving postoperative analgesia due to its ability to treat visceral and somatic pain. Spinally administered morphine acts primarily at the mu receptors in the spinal cord, whereas epidurally-administered morphine acts through spinal and supraspinal opioid receptors.[34] The duration of action of neuraxially administered morphine is between 12-24 hours. An extended-release epidural morphine has been developed; however, the increased monitoring requirements (48-hours) and the pharmacologic interaction with epidural local anesthetics limit its clinical use.[35] Patients who receive neuraxial opioids should receive scheduled parenteral non-steroidal anti-inflammatory agents (NSAIDs) postoperatively for treatment of visceral pain.

Parenteral Analgesia:
Intravenous narcotics and NSAIDs should be administered to patients who do not receive neuraxial opioids.

Transversus abdominis plane blockade:
The transversus abdominis plane (TAP) block is an adjuvant analgesic technique for post-cesarean delivery analgesia. Local anesthetic is deposited in the fascial plane between the transversus abdominis and the internal oblique. Several nerves lie in the transversus abdominis plane: the lower thoracic nerves (T7-T11), the subcostal nerve, and the two branches of the first lumbar nerve (the iliohypogastric and ilioinguinal nerves). While intrathecal morphine is the most efficacious technique for providing postoperative analgesia due to its ability to provide somatic as well as visceral analgesia, TAP blocks should be considered for women who undergo general anesthesia for cesarean delivery, for women who did not receive neuraxial morphine, and for those who experience breakthrough incisional pain despite having received neuraxial morphine.[36]

Complications of anesthesia:

Aspiration:

Aspiration is one of the feared complications of general anesthesia. While the incidence is decreasing, aspiration prophylaxis should be taken in all parturients undergoing cesarean delivery, even if under regional anesthesia, because of the risk of intraoperative conversion to general anesthesia.

Difficult Intubation:

Due to the physiologic changes of pregnancy (increased capillary engorgement with resultant decreased internal tracheal diameter), there is the potential for increased difficulty with intubation in pregnant patients.

Awareness:

The incidence of awareness following general anesthesia in the obstetric patient population is low, with current estimates of 0.1-0.2%.[37]

High spinal:

If a patient experiences a high spinal, it is important to assist with ventilation or intubate, maintain left uterine displacement, and treat hypotension until the level recedes.

Local anesthetic systemic toxicity:

Local anesthetic systemic toxicity (LAST) may occur in following the initiation of epidural anesthesia or with transversus abdominis plane blockade. Providers should be aware of the signs and symptoms of LAST and treatment algorithms.[38]

Neonatal depression:

Infants delivered under general anesthesia have a higher incidence of fetal acidemia and lower 1-minute Apgar scores than those delivered under neuraxial anesthesia.[17] With prolonged uterine incision-to-delivery intervals (>3-minutes), there is a higher incidence of acidosis and neonatal depression.[39]

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Management of Ambulatory Patients with Sleep Apnea: Application of Society of Anesthesia and Sleep Medicine Guidelines

Frances Chung MBBS, **Toronta, CA**

Obstructive sleep apnea (OSA) syndrome is the most common type of sleep disordered breathing and is characterized by recurrent apnea and hypopnea lasting ≥10 sec during sleep. In patients with OSA, there is an increased depression of pharyngeal muscle tone during sleep and anesthesia, resulting in a recurrent pattern of partial or complete upper airway obstruction with impaired respiration.[1] The prevalence of mild OSA is 1 in 4 males and 1 in 10 females;[2,3] moderate OSA is 1 in 9 males and 1 in 20 females.[4,5] A significant number of OSA patients are undiagnosed when they come for elective surgery.[6] Approximately 10-20% of surgical patients, of whom 80% had not been previously diagnosed with OSA, were found to be at high risk of OSA based on preoperative screening.[7,8] An increase in the prevalence of OSA as well as an increase in surgeries performed as ambulatory procedures poses a practical challenge to the anesthesiologist. OSA is associated with multiple comorbidities and the suitability of ambulatory surgery in OSA patients remains controversial due to the concerns of increased perioperative complications, including post-discharge death. At present, the evidence related to the safety of OSA patients for ambulatory surgery is limited. The American Society of Anesthesiologists (ASA),[9,10] and Society for Ambulatory Anesthesia (SAMBA)[11] have published guideline to emphasize the importance of proper patient selection and management of OSA patients for ambulatory surgery. In 2016, the Society of Anesthesia and Sleep Medicine has published guidelines on preoperative screening and assessment of patients with OSA.[12] In this lecture, we will determine whether a diagnosis of OSA would increase adverse events, identify the best tools for screening sleep apnea, summarize evidence on the effects of CPAP in surgical patients and the applications of SASM guideline on its applications to ambulatory surgical patients

Summary of Recommendations of Society of Anesthesia and Sleep Medicine (SASM) Guidelines[12]

- OSA patients undergoing procedures under anesthesia are at increased risk for perioperative complications compared to patients without the disease diagnosis. Identifying patients at high risk for OSA prior to surgery for targeted perioperative precautions and interventions may help to reduce perioperative patient complications.
- Screening tools help to risk stratify patients with suspected OSA with reasonable accuracy. Practice groups should consider making OSA screening part of standard pre-anesthetic evaluation.
- There is insufficient evidence in the current literature to support cancelling or delaying surgery for a formal diagnosis (laboratory or home polysomnography) in patients with suspected OSA, unless there is evidence of an associated significant or uncontrolled systemic disease or additional problems with ventilation or gas exchange.
- The patient and the health care team should be aware that both diagnosed OSA (whether treated, partially treated or untreated) and suspected OSA may be associated with increased postoperative morbidity.
- If available, consideration should be given to obtaining the results of the sleep study and, where applicable, the patient's recommended Positive Airway Pressure (PAP) setting before surgery.
- If resources allow, facilities should consider having PAP equipment for perioperative use, or have patients bring their own PAP equipment with them to the surgical facility.
- Additional evaluation to allow preoperative cardiopulmonary optimization should be considered in patients with diagnosed, partially treated/untreated and suspected OSA where there is indication of an associated significant or uncontrolled systemic disease or additional problems with ventilation or gas exchange such as: i) hypoventilation syndromes, ii) severe pulmonary hypertension, and iii) resting hypoxemia in the absence of other cardiopulmonary disease.

- Where management of comorbid conditions has been optimized, patients with diagnosed, partially treated, untreated OSA or with suspected OSA may proceed to surgery provided strategies for mitigation of postoperative complications are implemented.
- The risks and benefits of the decision should include consultation and discussion with the surgeon and the patient.
- The use of PAP therapy in previously undiagnosed but suspected OSA patients should be considered case by case. Due to the lack of evidence from randomized controlled trials, we cannot recommend its routine use.
- Continued use of PAP therapy at previously prescribed settings is recommended during periods of sleep while hospitalized, both preoperatively and postoperatively. Adjustments may need to be made to the settings to account for perioperative changes such as facial swelling, upper airway edema, fluid shifts, pharmacotherapy, and respiratory function.

Risk Factors & Pathophysiology[13] OSA is predisposed by various pathophysiological, demographic and lifestyle factors. These include anatomical abnormalities which may cause a mechanical changes in the airway lumen (e.g. craniofacial deformities, retrognathia, macroglossia), connective tissue diseases (e.g. Marfan syndrome), endocrine diseases (e.g., hypothyroidism, Cushing disease), male gender, neck circumference > 40 cm, age above 50 years, and lifestyle factors including alcohol consumption and smoking. The prevalence of OSA may be higher up to 78% in morbidly obese patients scheduled for bariatric surgery.[14] Obesity causes enlargement of soft tissue structures around the airway, and causing pharyngeal airway narrowing. Lung volumes are markedly reduced by increase in the abdominal fat mass. Reduction of lung volume may decrease longitudinal tracheal traction forces and pharyngeal wall tension, which causes narrowing of the airway. Visceral obesity is common in subjects with OSA. OSA is associated with various comorbidities such as myocardial ischemia, heart failure, hypertension, arrhythmias, metabolic syndrome, cerebrovascular disease, insulin resistance, gastroesophageal reflux, and obesity. Sympathetic activation is increased by apneic episodes, which prevents the normal nocturnal decline in blood pressure. Sleep apnea associated with obesity leads to increased sympathetic tone, hypertension, left ventricular hypertrophy, chronic hypoxemia, and exaggerated swings in intrathoracic pressure during obstructive episodes. OSA also causes an increase in right ventricular cavity size and wall thickness. OSA is one of the common reasons for resistance hypertention.[15] Though OSA is not a component of metabolic syndrome (central obesity, hypertension, hyperlipidemia and insulin resistance), there are experimental and clinical evidences to show the relationship between OSA and cardio-metabolic syndrome.[16] Anesthetics agents including sedative-hypnotics, opioids and muscle relaxants, exaggerate OSA-related airway instability, and worsen the apnea. Surgical stress response during the post-operative period significantly changes the sleep architecture.[17] This warrants a careful understanding of pathophysiology of OSA and the effects of anesthetic on the syndrome.

Obesity hypoventilation syndrome (OHS) is a condition with the triad of obesity, daytime hypoventilation and sleep disordered breathing without an alternative neuromuscular, mechanical or metabolic cause of hypoventilation.[18] OHS is often undiagnosed with a prevalence of 10-20% in obese patients with OSA and 0.15-0.3% among general adult population. Compared to eucapnic obese patients, OHS patients present with blunted central respiratory drive, severe upper airway obstruction, restrictive chest physiology, pulmonary hypertension and increased mortality and theyhave higher risks of perioperative complications.

Diagnostic Criteria of OSA[13] The gold standard for the diagnosis of OSA is the polysomnography or sleep study. The Apnea Hypopnea Index (AHI), defined as the average episode of abnormal breathing events per hour of sleep, which is used to diagnose and assess the severity of OSA. Diagnostic criteria for OSA by the American Academy of Sleep Medicine (AASM) requires either an AHI ≥15, or AHI ≥5 with symptoms, such as daytime sleepiness, loud snoring, or observed obstruction during sleep.[19] OSA severity is considered mild for AHI ≥5 to 15, moderate for AHI 15 to 30, and severe for AHI >30.

Perioperative complications of OSA patients undergoing surgery[20] A total of 52 studies were identified that reported on the association of OSA with select perioperative outcomes for surgeries under general or neuraxial anesthesia. In total, the included studies reported on 413,576 OSA patients (diagnosis by ICD-9 coding, polysomnography, chart or clinical diagnoses and screening questionnaires) and 8,557,044 control (non-OSA) patients.[20] The majority of the studies reported worse outcomes among patients with OSA compared to the control group.[20] Regarding mortality, 3 reported lower mortality in the OSA group and 1 study reported an increase in mortality among OSA patients. The decrease in mortality may be due to better monitoring and management of diagnosed OSA patients, protective effect of ischemic preconditioning and obesity paradox in OSA patients. The only study reporting increased mortality was a population-based database study which found an association between OSA diagnosis and increased mortality in patients undergoing revision knee or hip arthroplasties.

Recent outcome studies on inpatient surgeries have clearly shown serious cardiac and pulmonary complication in OSA patients, but the evidences are limited regarding postoperative outcome in OSA patients undergoing ambulatory surgery. The systematic review by SAMBA evaluated five prospective and two retrospective studies with various ambulatory surgical procedures including general surgery, orthopedic surgery, laparoscopic bariatric surgery, and upper airway surgery.[11] In this review, the postoperative outcome of 1491 OSA patients and 2036 low-risk OSA patients were compared with 2095 non-OSA patients.[11] None of these included studies reported any clinically significant adverse outcomes like the need for a surgical airway, hypoxic brain injury, longer discharge time, unanticipated hospital admission, or death. Also the systematic review showed that OSA patients had more incidence of postoperative hypoxemia, but there were no variation in the need for ventilatory assistance or reintubation.[11] In a prospective cohort study, those patients with greater possibility for OSA had more attempts of laryngoscopy, difficult laryngoscopic grade and fibreoptic intubation.[8] Also, the use of intraoperative ephedrine, metoprolol and labetalol were greater in OSA patients, but there was no difference in unanticipated hospital admission.[8] A recent study on 404 ambulatory head and neck procedures in OSA patients showed neither complication nor readmission.[21] A historical cohort study on 77,809 ambulatory surgical procedures did not identify any clinically significant increased rate of unplanned admission related with a prior diagnosis of 674 OSA patients.[22] The lack of increased postoperative complications in these studies may be due to careful selection of OSA patients for ambulatory surgery, use of CPAP and minimal opioids.

Preoperative Assessment for obstructive sleep apnea (Table 1)[12] Routine preoperative screening for OSA in patients presenting for surgery may identify the majority of the OSA patients, and may provide opportunities for heightened awareness and potential risk reduction by implementing appropriate preoperative, intraoperative and postoperative interventions.[12] Although the ultimate goal is to minimize risk of postoperative complication as much as feasible by ensuring that every patient with *suspected* OSA is identified, it is clear that such an approach will result in a challenging logistical, economic and clinical burden for healthcare providers.[12] Hence, a balance has to be struck between

the desire to minimize postoperative complications and the responsible use of resources. The realistic goal is to risk stratify those at particular risk, and suggest methods to prevent or treat problems without creating undue economic burden on the health care system.[12]

Screening tools such as STOP-Bang,[23-25] P-SAP,[26] Berlin[27] and ASA check list[27] can be used as preoperative screening tools to identify patients with suspected OSA.[12] These tools have been validated in the surgical population. The characteristics of each tool are shown in Table 2.[12] The STOP-Bang questionnaire was initially developed in the surgical patients but has been validated in various patient populations.[28] Patients with a STOP-Bang score of 0-2 is considered low risk, 3-4 as intermediate risk, and 5-8 as high risk of OSA.[23,24,29] The STOP-Bang questionnaire has the highest methodological validity and accuracy in predicting a diagnosis of OSA.[30,31] A STOP-Bang score of 5-8 identified patients with a high possibility of moderate-to-severe OSA.[29,32,33] The addition of serum bicarbonate level ≥ 28 mmol/L to a STOP-Bang score ≥ 3 increases the specificity for a preoperative diagnosis of OSA.[34] For obese or morbidly obese patients, a STOP-Bang score of 4 or greater can be used as a cut-off.[35] Patients with a higher STOP-Bang score are more likely to have increased postoperative complications. Also the Oxygen Desaturation Index (ODI) from a high resolution oximeter is sensitive and specific to identify undiagnosed sleep disordered breathing in the surgical patients.[36] ODI is a good predictor of AHI. The ODI ≥10 demonstrated a high sensitivity (93%) and reasonable specificity (75%) to detect moderate and severe OSA. Patients with preoperative mean overnight SpO2 <93%, or oxygen desaturation index >29 events/h were recently shown to be at higher risk for postoperative complicationss.[37] SASM guidelines indicate that additional evaluation for preoperative cardiopulmonary optimization should be considered in patients who have a high probability of having OSA and where there is indication of uncontrolled systemic conditions or additional problems with ventilation or gas exchange. These conditions include, but may not be limited to i) hypoventilation syndromes, ii) severe pulmonary hypertension, and iii) resting hypoxemia not attributable to other cardiopulmonary disease.[12]

Table 1 Summary of Recommendations for Screening to Identify Patients with Suspected OSA[12]

Recommendations	Level of Evidence	Grade of Recommendation
Patients with a diagnosis of OSA should be considered to be at increased risk for perioperative complications.	Moderate	Strong
Adult patients at risk for OSA should be identified before surgery.	Low	Weak
Screening tools such as STOP-Bang, P-SAP, Berlin and ASA checklist can be used as preoperative screening tools to identify patients with suspected OSA.	Moderate	Strong
Insufficient evidence exists to support cancelling or delaying surgery to formally diagnose OSA in those patients identified as being at high risk of OSA preoperatively, unless there is evidence of uncontrolled systemic disease or additional problems with ventilation or gas exchange.	Low	Weak

Adapted from Anesth Analg 2016;123:452-73

Table 2 Comparison of OSA screening tools in surgical patients[12]

	STOP-Bang Questionnaire (n=177)	Berlin questionnaire (n=177)	ASA Checklist (n=177)	P-SAP Score (n=511)
Sensitivity	83.6 (75.8-89.7)	68.9 (59.8–76.9)	72.1 (63.3–79.9)	93.9 (91.8–96.6)
Specificity	56.3 (42.3-69.6)	56.4 (42.3–69.7)	38.2 (25.4–52.3)	32.3 (23.2–46.7)
PPV*	81.0 (73.0-87.4)	77.9 (68.8–85.2)	72.1 (63.3–79.9)	10.0 (9.0–24.0)
NPV*	60.7 (46.1-74.1)	44.9 (32.9–57.4)	38.2 (25.4–52.3)	99.0 (98.0–99.0)
LR+	1.9 (1.40-2.61)	1.57 (1.17–2.36)	1.16 (0.94–1.51)	1.38 (1.37–1.39)
LR-	0.29 (0.18-0.46)	0.55 (0.39-0.79)	0.73 (0.47-1.13)	0.18 (0.16–0.21)
DOR	6.58 (3.03-14.36)	2.85 (1.48–5.50)	1.59 (0.81–3.13)	7.40 (6.48–8.45)
ROC	0.80	0.69	0.78	0.82

*Predictive values are highly dependent on the prevalence of OSA, which was 69% in the evaluation of STOP-Bang, Berlin and ASA checklist, and 7.1% for the P-SAP score. DOR diagnostic odds ratio, LR+ positive likelihood ratio, LR- negative likelihood ratio, NPV negative predictive value, PPV positive predictive value, ROC area under receiver operating characteristic curve. From Anesth Analg 2016;123:452-73

Best preoperative practices in patients who are diagnosed with OSA, non-adherent with prescribed therapy or have a high pre-test probability for OSA[12] As OSA remains undiagnosed in the majority of surgical patients, many patients will be identified as having a high probability for OSA for the first time during the preoperative screening process or on the day of surgery.[12] In addition, many patients with an established diagnosis of OSA either refuse to use, or are poorly adherent with the prescribed therapy. There are limited data to suggest that preoperative positive airway pressure (PAP) therapy, in the form of CPAP, auto titrated positive airway pressure (APAP) or bi-level positive airway pressure (BPAP) may improve perioperative outcomes.[38-41] The limited benefits of CPAP in surgical patients has been shown in a recent meta-analysis.[38] A diagnosis of OSA and a use of continuous positive airway pressure therapy were related with a reduction in postoperative complications especially cardiac arrest and shock.[40] Another study found that OSA patients with CPAP treatment have less cardio-respiratory complications than OSA without CPAP therapy.[41] All these evidences confirm that patients with OSA may safely undergo ambulatory surgery if the OSA patients are cautiously selected and receive focused perioperative care.

Table 3 Best preoperative practices for surgical patients with known OSA, adherent or non-adherent to PAP therapy or a high probability of OSA[12] Adapted from Anesth Analg 2016;123:452-73

Recommendations	Level of Evidence	Grade of Recommendation
Surgical patients with OSA who are adherent to PAP therapy		
The patient and the healthcare team should be aware that a diagnosis of OSA may be associated with increased postoperative morbidity	Low	Strong
Consideration should be given in obtaining the results of the sleep study and the recommended PAP setting before surgery	Low	Weak
Facilities should consider having PAP equipment available for perioperative use, or have the patient bring their own PAP equipment to the surgical facility	Low	Strong
Patients should continue to wear their PAP device at appropriate times during their stay in the hospital, both preoperatively and postoperatively	Moderate	Strong
Surgical patients with OSA but decline or are poorly adherent to PAP therapy		
The patient and the health care team should be aware that untreated OSA may be associated with increased postoperative morbidity.	Low	Strong
Consideration should be given to obtaining the results of the sleep study and the recommended PAP setting before surgery.	Low	Weak
Facilities should have PAP equipment for perioperative use, or have the patient bring their own PAP equipment with them to the surgical facility.	Low	Strong
Additional evaluation for preoperative cardiopulmonary optimization should be considered in patients with known OSA who are non-adherent or poorly adherent to PAP therapy and have uncontrolled systemic conditions or additional problems with ventilation or gas exchange such as: i) hypoventilation syndromes, ii) severe pulmonary hypertension, and iii) resting hypoxemia in the absence of other cardiopulmonary disease.	Low	Weak
Untreated OSA patients with optimized co-morbid conditions may proceed to surgery provided strategies for mitigation of postoperative complications are implemented. The risks and benefits of the decision should include consultation with the surgeon and the patient.	Low	Weak
Patients should be encouraged to wear their PAP device at appropriate times during their stay in the hospital, both preoperatively and postoperatively	Moderate	Strong
Surgical patients who have a high probability for OSA		
The patient and the healthcare team should be aware that a high probability of OSA may increase postoperative morbidity.	Low	Strong
Additional evaluation for preoperative cardiopulmonary optimization should be considered in patients who have a high probability of having OSA and have uncontrolled systemic conditions or additional problems with ventilation or gas exchange such as: i) hypoventilation syndromes, ii) severe pulmonary hypertension, and (iii) resting hypoxemia in the absence of other cardiopulmonary disease.	Low	Weak
Patients who have a high probability of having OSA may proceed to surgery in the same manner as those with a confirmed diagnosis, provided strategies for mitigation of postoperative complications are implemented. Alternatively, they may be referred for further evaluation and treatment. The risks and benefits of the decision should include consultation with the surgeon and the patient.	Low	Weak
Patients should be advised to notify their primary medical provider that they were found to have a high probability of having OSA, thus allowing for appropriate referral for further evaluation.	Low	Weak

Patient selection for ambulatory surgery[13] In 2006 & 2014 ASA published guidelines on the perioperative management of OSA patients,[9,10] based on the severity of sleep apnea, invasiveness of surgery, type of anesthesia and the need of postoperative opioids. Based on a systematic review of recent evidences, SAMBA has

recommended a consensus statement on the preoperative selection of patients with OSA for ambulatory surgery.[11] According to SAMBA guideline, patients with diagnosis of OSA and compliant with continuous positive airway pressure (CPAP), have optimized comorbid conditions and minimal postoperative opioids requirements can be considered for ambulatory surgery (Fig. 1).[11] But, patients who are noncompliant with CPAP may not be appropriate for ambulatory surgery. At the same time patients with a presumed diagnosis of OSA based on the screening tool and optimized comorbid conditions may be considered for ambulatory surgery, if postoperative pain relief can be managed predominantly with non-opioid analgesic techniques. In contrast to the ASA OSA guidelines, laparoscopic upper abdominal surgeries like gastric banding may be safely performed on a day surgery basis provided the perioperative precautions are followed. Because of limited evidence, no guidance was provided for OSA patients undergoing upper airway surgery. A recent systematic review on obese patients selection for ambulatory surgery showed that the literature lacks enough information to make recommendations regarding the selection of the obese patients for ambulatory surgery.[42] The super obese patients with BMI >50 kg/m^2 are at increased risk for perioperative complications, while patients with lower BMI do not present any increased risk as long as the comorbidities are optimized before surgery.[42]

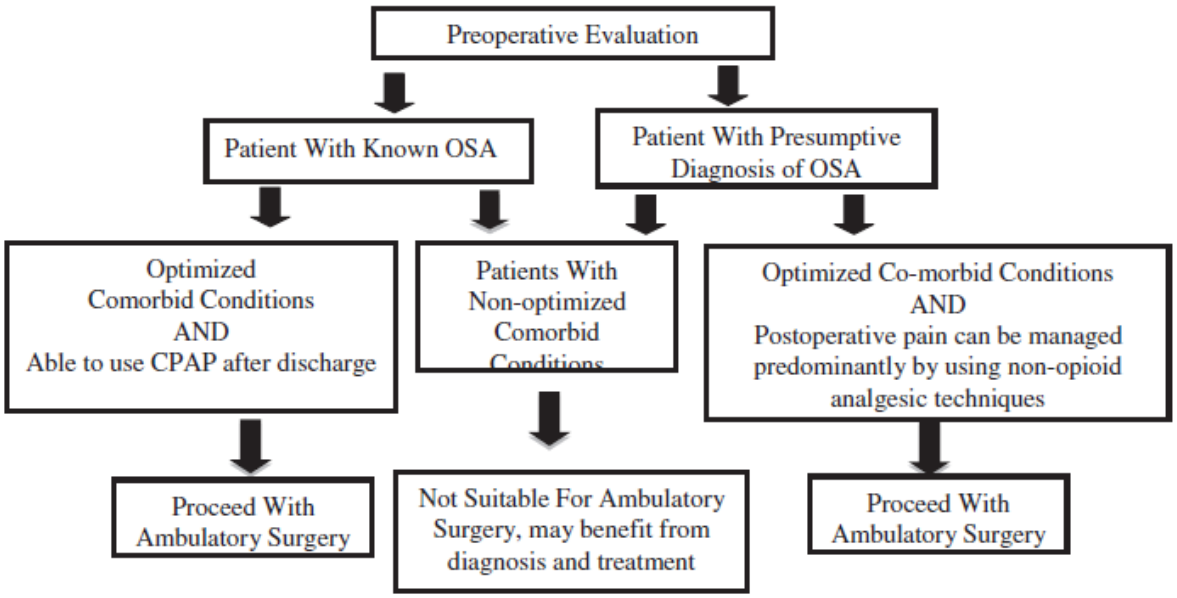
Post-operative disposition & unplanned admission after ambulatory surgery Diagnosed or suspected OSA patients, receiving general anesthesia should have extended monitoring after they have met the modified Aldrete criteria for discharge.[10] The incidence of recurrent respiratory events in PACU is an indication for continuous postoperative monitoring.[43] The respiratory events are episodes of apnea ≥ 10 sec, bradypnea <8 breaths/min, pain-sedation mismatch, or repeated O2 desaturation <90%. Repeated occurrence of any of the above events is considered as recurrent PACU respiratory events. OSA patients with recurrent respiratory events have an increased risk of postoperative respiratory complications.[43] These patients may require postoperative PAP therapy with monitoring.[12] Ambulatory surgical centers that handle OSA patients should have the backup to manage postoperative complications related with OSA and an agreement with an appropriate inpatient facility. Postoperative complications may be the result of an imbalance between enhanced pain processes and increased sensitivity to anesthetics and/or opioids in patients with some specific OSA phenotypes.[44-45] Postoperative disturbances of sleep disordered breathing can occur in the postoperative nights at home.[17,46] The anesthesiologist and surgeon should agree on post-operative analgesic medication and patients should be advised to use acetaminophen, NSAIDs, and COX2 inhibitors rather than opioids. Patients should be educated to sleep in a semi-upright position and to apply their PAP devices when sleeping, even during the daytime. It is necessary to educate surgeons, patients, and their family regarding the need for increased vigilance after discharge home.

Conclusion

In recent years, there is a better understanding about the effect of anesthetics on post-operative sleep architecture in OSA patients. This warrants a careful selection of patients for ambulatory surgery with specific protocol and risk mitigation is imperative to avoid cancellations and complications. Educating patients and the health care team will improve the perioperative outcome. With appropriate screening and algorithm based management, the majority of the ambulatory surgical procedure may be done safely in patients with OSA.

Figure 1: Decision making in preoperative selection of a patient with OSA for ambulatory surgery

Adapted from SAMBA guideline Anesth Analg 2012; 115: 1060-8



Material adapted from Chung F et al Society of Anesthesia and Sleep Medicine Guideline on preoperative screening and assessment of patients with OSA. *Anesth Analg* 2016;123:452-73 and Raveendran R, Chung F. Ambulatory anesthesia for patients with sleep apnea. Ambulatory Anesthesia 2015; 2:143-51 http:/dx.doi.org/10.2147/AA.S63819

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ANESTHESIOLOGY 2017
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Epidemic of Opioid Prescriptions in USA: update of 2017

Asokumar Buvanendran **Chicago, IL**

The RCL is to provide appropriate opioid prescribing suggestions. It is the result of a review of the expert review, evidence based research, and clinical practice experience. Nearly one third of the United States population suffers with chronic pain. Pain severe enough to limit activity is present in approximately 25 million Americans; the societal costs of chronic pain are astronomical, estimated at over $600 billion alone in annual lost work productivity and medical expenses.[1] These costs (including direct medical costs and lost wages) are higher than those for heart disease, cancer, and diabetes combined.

Physicians who care for patients with chronic, non-cancer pain must balance many important considerations when commencing with pain management treatment and most importantly opioid therapy. While opioids can be effective for well-selected patients, many may not obtain sustained benefit from this class of medications and many may potentially have the increased risk of inappropriate misuse or abuse due to opioid dependence and addiction.[2] Opioid prescriptions increased dramatically from the 1990's to 2004 and have remained high in subsequent years[3] with nearly 220 million prescriptions written in 2011, compared to 76 million in 1991.[4] Simultaneously, a dramatic increase in opioid addiction, overdose and death is occurring.[5,6] It is important to recognize that predominate source of opioids misused by patients is leftover or surplus prescription medication. To understand where these prescription opioids are coming from, a 2013 national survey reported that 53% of those abusing prescription painkillers received them from a friend or relative; and further, the source of the prescription was a single doctor in 84% of these cases.[7]

Despite lowering the risk of subsequent overdose, discontinuation of opioid therapy after the initial opioid overdose often does not consistently occur in the majority of cases.[8] Clinicians from all specialties have the responsibility to address this issue and also understand the inadvertent role that they have contributed to the rise in opioid prescriptions. The greatest number of opioid prescriptions are written by primary care physicians and advanced practice providers, and the highest concentration on opioid prescribing is in pain management, physical medicine and rehabilitation, and anesthesiology.[9] The dramatic increase in opioid prescribing has contributed to the prevalence of prescription drug abuse in the United States. It is imperative that

opioid prescribers must carefully weigh risks versus benefits of opioids for chronic, benign pain and contemplate important questions such as patient selection, initiation and titration of opioids, establishing effectiveness, random drug testing, collaboration with specialists and other caregivers, and cessation of opioids when indicated.

A systematic, multimodal, and comprehensive approach to opioid prescribing is necessary to optimize outcomes for this patient population while minimizing the risk of opioid related long-term disability, morbidity, mortality, abuse and diversion. Failure to recognize the complexity of chronic pain and the need for comprehensive care may potentially lead to significant risk and ineffective treatment.

Prior to Initiation of Opioid Therapy

Patient assessment begins with a comprehensive history and physical exam to: (1) determine the diagnosis for the patient's pain complaint which may involve a detailed assessment with various diagnostic tests, (2) evaluate how the pain is affecting the patient's quality of life and function and ability to enjoy life, (3) characterize co-morbidities and psychosocial factors which could affect the choice of therapies, (4) assess prior approaches to pain management and their effectiveness, and (5) establish a basis for developing a treatment plan to help reduce the patient's pain and return them a desired level of functioning and quality of life and ability to enjoy life as per CDC recommendations for pain assessment, including documentation of pain intensity, aggravating and relieving factors, history of pain treatments and level of functioning. Providers must bear in mind that patient's pain and response to treatment will vary over time and according to genetic, psychosocial and cultural factors.

As such, pain is a subjective and dynamic experience and at present, physicians lack options to objectively quantify pain severity other than by patient reported measures such as pain intensity and its impact through pain interference. It is critical to understand that clinicians need to demonstrate empathy in accepting the patient's report of pain and simultaneously determine if the magnitude and characteristics of the pain complaint is commensurate with causative factors and if these have been adequately evaluated and treated with non-opioid therapy. In addition to non-opioid medication therapy, many pain treatments can be employed before initiating opioids, such as physical/occupational therapy, psychological approaches (e.g. cognitive behavioral therapy, biofeedback and relaxation therapy), complementary treatments, alternative medicine

treatments, chiropractic manipulation, osteopathic treatment, and interventional pain treatments such as epidural steroid injections, radiofrequency denervation and spinal cord stimulation (SCS). Efficacy of SCS has been demonstrated in RCTs and can be of value in selected chronic pain patients.

If opioid therapy is considered, patients at risk for abuse and opioid related complications should be carefully and meticulously identified including those with a history of current or former substance abuse, misuse, or under-treated mental health disorders (e.g. depression, anxiety, post-traumatic stress disorder). Additionally, a comprehensive assessment should be completed of all social factors that may impact pain management including: employment, job satisfaction, marital history, social network, and history of legal problems. Patients with multiple co-morbidities and concurrent use of medications likely to interact with opioids may also be poor candidates. In particular, central nervous system depressants which include benzodiazepines can act synergistically with opioids and place the patient at risk for adverse respiratory outcomes. Additional assessment may be necessary to determine the appropriateness of opioid therapy which may include testing for important co-morbidities such as respiratory conditions, liver dysfunction, renal insufficiency, sleep apnea (both obstructive and central), cardiac disease, and medication allergies. The geriatric population is a vulnerable group that needs special attention if opioid therapy is considered. In general, lower starting dose and longer dosing intervals are advised until patient response is assessed.

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ANESTHESIOLOGY 2017
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Coexisting Disease in Infants and Children: Navigating the Difficult Pathway to the Operating Room

Linda J. Mason, M.D. **Loma Linda, California**

ASTHMA

Asthma is the most common chronic disease in children. All anesthesiologists routinely encounter children with asthma and will likely encounter an increasing number of these children in the future. A recent governmental report finds that the asthma prevalence in the United States is increasing; currently at 9.5% of children aged 0-17.[1] Children < 3 years old frequently have episodic respiratory symptoms (cough, wheezing), but most of these children do not go on to have a clinical diagnosis of asthma.[2] Asthma is defined by chronic inflammation of the airways, associated with airway hyper-responsiveness, which leads to recurring episodes of wheezing, coughing, breathlessness, and chest tightness and reversible airflow obstruction within the lung. Contributing factors include genetic predisposition, atopy, and respiratory syncytial virus infection in infancy. Asthma patients carry a small but significantly increased risk for operative and postoperative complications.[3]

Pharmacotherapy for Asthma

β-Adrenergic agonists -β-adrenergic agonists are commonly used to provide rapid relief of acute bronchospasm (short acting β-agonists, SABAs) and are also used for chronic treatment (long-acting β-agonists, LABAs) but only in combination with inhaled corticosteroids. The inhaled β-2 adrenergic agents have a wide therapeutic window with a toxic dose that is far greater than their therapeutic dose. When these drugs activate the β-2 receptor, adenyl cyclase increases cAMP levels, which causes smooth muscle relaxation and increased mucocilliary clearance.[4] Although they may be administered by oral or intravenous (IV) routes, inhalation administration provides faster peak bronchodilatation and fewer systemic side effects.[5]

Corticosteroids - Inhaled corticosteroids are the foundation of treatment for asthma because they target the inflammation that characterizes the disease. They should be seen as "controller" medications because they do not cure the disease and their efficacy depends on consistent, appropriate administration. They have been shown to reduce airway reactivity, inhibit inflammatory cell migration and activation, and block reactions to allergens.[6] High dose inhaled corticosteroids may have some systemic side effects, but the common side effects of oral thrush and hoarseness seen in adults are rare in children. Systemic corticosteroids, either oral or parenteral, are reserved for severe, uncontrolled asthma.

Leukotriene Pathway Modifiers - Leukotriene modifiers are most commonly used as second-line controller medications. Leukotrienes are produced by mast cells, eosinophils and basophils inducing edema, stimulation of airway secretions, and smooth muscle proliferation (by a nonhistamine mechanism).[7] These orally administered drugs are particularly useful in several specific areas, including: exercise-induced, intermittent (viral-induced), and aspirin-induced asthma.[7]

Anticholinergics - Ipratropium bromide inhibits mucous hypersecretion and decreases reflex bronchoconstriction by targeting airway muscarinic cholinergic receptors. It may be administered by metered dose inhaler (MDI) or nebulizer and is a quaternary amine with no significant systemic absorption or side effects. Ipratropium is rarely used in chronic management of pediatric asthma patients. Several systematic reviews confirm its benefit in the setting of severe acute asthma when combined with other treatments.[8]

Methylxanthines - Theophylline functions as a mild bronchodilator and anti-inflammatory. Because of the fact that its effect is less than that of low-dose inhaled corticosteroids, it is seldom used as first-line therapy. It has proven effective as a rescue medication in status asthmaticus.[9] Because theophylline has a very low therapeutic index serum monitoring is essential. Side effects include nausea, vomiting, headache and seizures.

Preanesthetic Evaluation

Pediatric asthmatic patients require careful preoperative evaluation and preparation. Essential points to review in the preoperative evaluation are the level of asthma control and the current medication regimen. In addition, review of the level of activity, use of rescue medications, hospital visits (tracheal intubation or IV infusions required), allergies, and previous anesthetic history are important. Also an inquiry regarding cough and sputum production should occur. Although otherwise healthy children can often be anesthetized safely during an acute upper respiratory infection (URI) the risk of bronchospasm in asthmatics is very high.[10,11] They should ideally be postponed 4-6 weeks after such an event. Physical examination should include vital signs, assessment for wheezing, cough, type of breath sounds, use of accessory muscles, and level of hydration. Room air oxygen saturation is useful as a baseline and for determining preexisting hypoxemia but other laboratory data are not usually necessary.

The diagnoses of atopy/eczema and allergic rhinitis often go hand in hand with a diagnosis of asthma as they are all thought to be conditions of chronic inflammation.[12] A family history of asthma and atopy also contributes to intraoperative respiratory complications.[10] As in adults, significant gastroesophageal reflux disease can often be a trigger for asthma symptoms.[13] Obese patients present a variety of anesthetic challenges. Relevant to this discussion is not only the association of obesity and asthma, but also the increase in intraoperative bronchospasm seen in obese children even without a diagnosis of asthma.[14] Exposure to second-hand smoke should be considered a risk factor for poor asthma control, as well as, an independent risk factor for adverse respiratory events in children under general anesthesia.[15]

Risk Factor Optimization

Preoperative preparation for a controlled asthmatic may include a use of an inhaled β-2 adrenergic agonist 1-2 hours prior to surgery. For moderately controlled asthma, additional optimization with an inhaled corticosteroid and regular use of inhaled β-2 agonists 1 week prior to surgery can be instituted. Poorly controlled asthmatics may need addition of one of the following: oral prednisone 1 mg kg $^{-1}$day^{-1} (60 mg max) 3-5 days before surgery, oral dexamethasone 0.6 mg kg^{-1} (16 mg max) or oral methylprednisolone 1 mg kg^{-1} for 48 hours prior to surgery.[16]

Perioperative Management

Immediate Preanesthetic Preparation - Patients should continue all their controller medications as normal on the day of surgery. An extra dose of SABA may be efficacious if deemed necessary from the preoperative evaluation. Giving a routine "extra dose" (in addition to the patient's scheduled dose) to all asthmatics regardless of the level of control may not be warranted, although, the beneficial effect of SABAs on reflex bronchoconstriction in response to tracheal intubation is clear.[17,18] Premedication with oral midazolam, 0.5-1 mg kg^{-1}, is safe in asthmatics, and may be indicated since anxiety may precipitate acute bronchospasm.[19] The use of systemic corticosteroids in the last 6 months or high-dose inhaled corticosteroids is an indication for stress dose coverage.[6] If indicated by the preoperative evaluation, it is still not too late to give IV corticosteroids as their beneficial effect will extend into the postoperative period.

Anesthetic management - If an IV catheter is in place prior to induction several medications can be given to diminish the response to tracheal intubation. Lidocaine may prevent reflex bronchoconstriction and has little toxicity at a dose of 1-1.5 mg kg^{-1} IV, 1-3 minutes prior to tracheal intubation.[20] Direct spraying of the airway may trigger airway reactivity so the IV route is preferable.[21] IV glycopyrrolate or atropine given long with an IV induction or after an inhalational induction may decrease secretions and provide additional bronchodilatation prior to tracheal intubation via their effect at muscarinic receptors.

The choice between IV versus inhalational induction is often influenced by multiple clinical factors. There is little compelling evidence to suggest one technique over another in asthmatic children. If an IV induction is chosen, propofol is the IV induction agent of choice in hemodynamically stable asthmatic patients. It has been shown in multiple studies to attenuate the bronchospastic response to tracheal intubation, both in asthmatic and non-asthmatic patients.[22,23] Its effect is likely mediated by suppression of vagally mediated stimulation of bronchial muscarinic receptors.[24] Recent animal research suggests that propofol may mediate bronchodilation via other pathways including airway smooth muscle GABA receptors and diminishing the effect of tachykinins on airway smooth muscle.[25] Neither thiopental nor etomidate mediate the bronchospastic response to tracheal intubation as effectively as propofol.[23] Ketamine is the induction agent of choice in hemodynamically unstable asthmatic patients. It likely produces smooth muscle relaxation and bronchodilatation directly, via release of catecholamines, and vagally mediated mechanisms, although, its bronchoprotective effect is not as pronounced as that of propofol.[24] Its mucous stimulating effects can be ameliorated by pre-treatment with atropine or glycopyrrolate.

Volatile anesthetics have long been known to depress airway reflexes to tracheal intubation and cause direct airway smooth muscle relaxation.[26] Sevoflurane seems to have the most pronounced effect of all the inhalational anesthetics and is the agent of choice for mask induction.[27] As a word of caution: in children with asthma, tracheal intubation with sevoflurane as the sole anesthetic (even at 5% concentration) causes an increase in respiratory system resistance as compared to non-asthmatic children.[28] It is important to recognize that having an asthmatic child use a SABA prior to induction with sevoflurane can decrease the risk of increased airway resistance and bronchospasm that occurs with tracheal intubation.[17] During maintenance of anesthesia, children with asthma have shown low airway resistance with a propofol infusion, but in most asthmatic children switching to sevoflurane further improved this effect. In contrast, a switch to desflurane caused elevation in airway resistance in these susceptible children.[29] Although some have questioned the *mechanism* by which desflurane increases airway resistance, it is clear that at typical, MAC-equivalent doses desflurane does increase airway resistance.[30]

The decision regarding airway management is likewise influenced by multiple clinical factors. As tracheal intubation is one of the most potent triggers for bronchospasm, choosing a laryngeal mask airway (LMA) or simple mask may be useful.[31] Little research defines the risks for asthmatic children in regard to tracheal intubation versus

LMA but children with recent URI may benefit from the use of an LMA.[32] Should tracheal intubation be required, the use of cuffed tracheal tubes allows for avoidance of multiple intubations due to air leak, more reliable end-tidal CO_2 waveform monitoring, and the use of lower fresh gas flows.[33] Regional anesthesia should be considered whenever possible to avoid airway manipulation, but may not be feasible for the uncooperative pediatric patient or for certain surgical situations.

Non-histamine releasing muscle relaxants such as rocuronium, vecuronium, and cisatracurium are acceptable for use in children with asthma. Reversal of neuromuscular blockade with acetylcholinesterase inhibitors (e.g. neostigmine or edrophonium) may be undertaken with caution in asthmatics but carries the risk of residual neuromuscular blockade and muscarinic side effects including bronchospasm.

Airway irritation should be minimized by humidification of inspired gases. Stimulation of the trachea by suctioning should also be minimized and performed only with deep levels of anesthesia. During mechanical ventilation, inspiratory pressures should be kept low and the expiratory time lengthened. Careful attention should be paid to the avoidance of intrinsically developed positive end-expiratory pressure (PEEP).[34] On a theoretical basis, deep extubation should decrease the risk of bronchospasm evoked by coughing on the tracheal tube; however, little research has been done to answer this question for asthmatic children.[35]

Treatment of Intraoperative Bronchospasm -Treatment of intraoperative bronchospasm in children presents a unique set of problems, particularly when the bronchospasm is severe. Inhaled β-2 agonists are the treatment of choice, yet the delivery of inhaled medications via small tracheal tubes is difficult. Previous research has shown that only 2.5-12.3% of the dose of albuterol by MDI into 3.0-6.0 mm ID tracheal tubes is delivered to the patient.[36] Resourceful anesthesiologists have sought ways to overcome this problem in various ways, including actuating the MDI canister into a long, 19G IV catheter advanced out of the end of the tracheal tube.[36] Although this method increases delivery of albuterol 10-fold, delivery of concentrated medication and other components of the MDI may cause damage to the airway.[37] Both MDI spacers and nebulizers have been modified in a variety of ways to fit into a ventilator circuit. Each technique has advantages and disadvantages but in the operating room environment. simplicity and rapidity of deployment seem to favor MDIs with spacers.

Occasionally, severe bronchospasm can make it difficult to deliver any inhaled medications necessitating an alternate route of administration. IV anticholinergic medications should be given and additional steroids (up to 2 mg kg^{-1} of hydrocortisone or methylprednisolone) may not have immediate effect but can aid in avoiding postoperative bronchospasm. Intravenous or subcutaneous β-agonists in the form of terbutaline (10 mcg kg^{-1} over 10 min), epinephrine, or isoproterenol, may be used if previous therapy is unsuccessful in terminating the bronchospasm.[38,39] IV theophylline (5-7 mg kg^{-1} over 20 minutes) can be added in refractory situations.[9,40] Magnesium (50 mg kg^{-1} over 20 minutes) has been shown to benefit children with severe asthma already treated with β-agonists and corticosteroids.[41] The final option for patients failing all the previously described treatments is extra-corporeal membrane oxygenation. It has been used successfully, with minimal neurological outcomes, to treat refractory asthma in children.[42]

Obstructive Sleep Apnea

Sleep apnea is a sleep-related breathing disorder in children characterized by a periodic cessation of air exchange, with apnea episodes lasting >10 seconds and an apnea/hypopnea index (AHI) – total number of obstructive episodes per hour of sleep >5.[43] Air flow cessation is confirmed by auscultation or oxygen desaturation <92%. Types of sleep apnea include central (absent gas flow, lack of respiratory effort), obstructive (absent gas flow, upper airway obstruction and paradoxical movement of rib cage and abdominal muscles) and mixed (due to both CNS defect and obstructive problems). A new screening tool has been recommended for use by primary care physicians in evaluating pediatric patients with possible OSA. It is call the "I'M SLEEPY questionnaire (to be answered by parents and includes 8 questions which gives the provider a score that can help them make a decision about considering referral for a sleep medicine consultation.[44] Diagnosis is made by clinical assessment (a history of snoring and restless sleep), nocturnal pulse oximetry or polysomnography studies (PSG).

Obstructive sleep apnea syndrome (OSAS) is manifest by episodes that disturb sleep and ventilation. These episodes occur more frequently during REM sleep and increase in frequency as more time is spent in REM sleep periods as the night progresses. OSAS occurs in children of all ages (about 2% of all children) but more commonly in children 3-7 years of age. It occurs equally among boys and girls but the prevalence may be higher in African American individuals.[45] Childhood obesity is increasing in modern societies and OSAS is increased in children with obesity. Signs of OSAS are sleep disturbances (including daytime sleepiness), failure to thrive from poor intake due to tonsillar hypertrophy, speech disorders, and decreased size (decreased growth hormone release during disturbed REM sleep). This syndrome can cause significant cardiac, pulmonary and CNS impairment due to chronic oxygen desaturation. In children with OSAS and morbid obesity the incidence of hypertension and diabetes are seen at much higher rates. Therefore it is important that prior to surgery that the cardiovascular status be evaluated in this

group of children. Although right ventricular dysfunction is classic, biventricular hypertrophy can develop. It is more likely to be seen in patients with severe OSAS but has been reported in patients with only mild OSAS.[46] Pulmonary vasoconstriction can increase pulmonary vascular resistance with resultant decrease in cardiac output due to cor pulmonale. Relief of the tonsillar/adenoidal obstruction can reverse many of these problems and prevent progression of others (pulmonary hypertension and cor pulmonale). Cardiac evaluation is recommended for any child with signs of right ventricular dysfunction, systemic hypertension or multiple episodes of desaturation below 70%. Electrocardiogram and chest radiograph are not sensitive tools; echocardiography is recommended.[47]

Patients that are at high risk for postoperative upper airway obstruction after tonsillectomy and/or adenoidectomy for OSAS include age < 2 yr, craniofacial anomalies, failure to thrive, hypotonia, morbid obesity, previous upper airway trauma, cor pulmonale, a polysomnogram with a respiratory distress index (RDI) > 40 or O_2 saturation nadir <70% or patients undergoing an additional uvulopalato pharyngoplasty (UPPP).[48] If upper airway obstruction occurs postoperatively in these patients, nasal CPAP/BIPAP should be considered as a therapeutic intervention.[48] In a recent analysis, children at risk for OSAS had more postoperative adverse events associated with apnea while all other indications for tonsillectomy had a large proportion of adverse events attributed to hemorrhage.[49]

The American Academy of Pediatrics Clinical Practice Guidelines[45] give the following recommendations for inpatient monitoring in patients at high risk for postoperative complications that have OSAS and are undergoing adenotonsillectomy. These include:

Age younger than 3 years
Severe OSAS on polysomnography
Cardiac complications of OSAS (eg right ventricular hypertrophy)
Recent respiratory infection
Craniofacial disorders
Neuromuscular disorders
Cerebral palsy
Down syndrome
Failure to thrive
Obesity
Prematurity
Sickle cell disease
Central hypoventilation syndromes
Genetic/metabolic/storage disease
Chronic lung disease

As far as outpatient surgery for adenotonsillectomy in patients with OSAS, children age 1-18 years without underlying medical conditions, neuromuscular disease or craniofacial abnormalities with mild sleep apnea (<15 obstructive events per hour) will have improvement of their airway obstruction documented by polysomnography the night of surgery and do not need to be monitored intensively. In these patients a smaller number of obstructive events and fewer severe oxygen desaturations occurred on the operative night.[50] Based on this and other studies it is possible to consider discharge to home for children age 3-12 years if they meet these criteria. However, in children with severe obstructive sleep apnea (AHI >16.4 events/hr, SaO_2 <85%) obstructive events occurred more frequently on the first night after adenotonsillectomy suggesting overnight monitoring with pulse oximetry is indicated.[51]

OSAS patients with preoperative nocturnal oximetry oxygen saturation of 80% or less had an increase from 20% of postoperative respiratory complications to 50%. Usually these children were younger (<2 years) and had an associated medical condition.[52] Sixty percent of OSAS patients requiring urgent adenotonsillectomy had postoperative respiratory complications. Risk factors for respiratory complications were again an associated medical condition and preoperative nocturnal oxygen saturation nadir less than 80%. Atropine administration at induction decreased the risk of postoperative respiratory complications. There was an 11.1% incidence of reintubation and a 9.3% incidence of postoperative pneumonia in this urgent adenotonsillectomy group.[53]

Children with severe OSAS who had adenotonsillectomy in the morning were less likely to have postoperative desaturation than those who were operated in the afternoon.[54] The shortened time interval between postoperative morphine dosing and bedtime may contribute to the incidence of postoperative desaturation because of an exaggerated respiratory depressive response to opioids which has been reported in children with severe OSAS.[55] There is a strong possibility that the combination of opioids and sleep promote desaturation in these patients.

Children with OSAS in general may have a diminished ventilatory response to CO_2 rebreathing compared with normal children.[56] Therefore drugs known to cause ventilatory depression (sedative hypnotics, anxiolytics, narcotics and inhaled agents) must be used judiciously in these patients as they may be more sensitive to their effects. Preoperative administration of midazolam 0.5 mg/kg in 70 children undergoing adenotonsillectomy for OSAS (diagnosed as severe in 40% of subjects by polysomnography) resulted in 2 children having respiratory events; one had a self limited desaturation event before surgery and one had a postoperative obstruction with desaturation requiring a nasal airway.[57] Patients with OSAS can receive sedatives but require monitoring.

During inhalational induction of anesthesia, children with OSAS are at a high risk for airway obstruction due to relaxation of the genioglossus muscle. Positioning in an upright or lateral position, use of jaw thrust maneuver,

delivery of positive pressure by face mask and placement of an oral airway may aid in relieving the obstruction.[58] Once anesthesia is induced and intravenous access is established, a single dose of IV propofol 1.5-2 mg/kg (lean body weight) may facilitate tracheal intubation.[59]

Children with OSAS usually need pain medication after surgery yet chronic hypoxemia renders them more susceptible to the respiratory depressant effects of opioids.[60] Younger aged patients or those with preoperative nocturnal oxygen saturation less than 85% had reduced morphine requirement possibly due to up-regulation of central opioid receptors consequent to recurrent hypoxemia.[61] Children whose minimum nocturnal saturation was less than 85% required one half of the dose of opioids for similar pain scores after T & A surgery compared with children whose minimal saturation was 85% or greater.[62]

One technique for opioid administration is that after tracheal intubation and spontaneous ventilation is restored, small incremental aliquots of IV morphine (10-20 ug/kg) or fentanyl (0.2-0.5 ug/kg) can be administered. If apnea occurs after the first aliquot of opioid, the child may be considered opioid sensitive. If they continue to breathe additional increments up to the standard total dose of 50-100 ug/kg of morphine can be administerd.[59] Drugs for pain management to decrease opioid use include ketamine 0.1 mg/kg[63] IV, or peritonsillar infiltration of ketamine 0.5 to 1 mg/kg given 3 minutes before surgery[64], dexamethasone 0.0625-1 mg/kg (maximum 25 mg) with an average dose of 0.5 mg/kg and IV acetaminophen 15 mg/kg (maximum 75 mg/kg/d, children 2-12 years).[65,66]

Concern over dexamethasone use in tonsillectomy patients in respect to postoperative bleeding was raised in an article that compared three doses of dexamethasone 0.05 mg/kg, 0.15 mg/kg and 0.5 mg/kg. The primary objective was a decrease in nausea and vomiting and the secondary objective was postoperative analgesia. Regardless of the dose, children who received dexamethasone needed less rescue analgesia and antiemetics, however the larger dose 0.5 mg/kg was associated with the highest decrease in postoperative nausea and vomiting (PONV). Of concern was that both the 0.5 mg/kg dose and the 0.05 mg/kg dose of dexamethasone were associated with a higher incidence of postoperative bleeding. The problem with this study was the lack of standardization of surgeon, surgical technique and use of nonsteroidal antinflammatory drugs. This study has too many flaws to change the practice of giving dexamethasone to tonsillectomy patients and needs to be repeated with bleeding as a primary outcome in relation to dexamethasone use.[67] In a more recent retrospective review of 2788 children age 2-18 undergoing tonsillectomy were given either 0.5 mg/kg or 1.0 mg/kg of dexamethasone. The study was adjusted for age, sex, primary diagnosis (sleep related disorder and infectious tonsillitis) and surgical technique, either extracapsular electrosurgical tonsillectomy, extracapsular radiofrequency ablation tonsillectomy or intracapsular microdebrider tonsillectomy. Perioperative dexamethasone administration was not associated with a dose dependent elevation of postoperative hemorrhage.[68] A recent Cochrane review of 19 randomized placebo controlled, double blinded studies conclude that children receiving a single intraoperative dose of dexamethasone (dose range 0.15-0.5 mg/kg) were half as likely to vomit in the first 24 hours and had less pain than the placebo group.[69]

A recent report of adenotonsillectomy for children who demonstrated recurrent episodes of profound hypoxemia (<80% saturation) during the perioperative sleep study demonstrated that a decrease in major medical respiratory interventions by >50% was accomplished by administration of dexamethasone 0.3 mg/kg (maximum 10 mg) and the titration of morphine 0.02 mg/kg.[70]

Nonsteroidal anti-inflammatory drugs (NSAIDS) have been avoided in post-tonsillectomy patients because of reports of association postoperative bleeding. However, a systematic review did not find an increased risk of reoperation for bleeding and found less vomiting when NSAIDS were part of an analgesic regimen.[71] The use of NSAIDS after attainment of hemostasis is reasonable.[72] A new study with administration of 10 mg/kg of IV ibuprofen prior to tonsillectomy, showed a significant narcotic sparing effect with no increase in bleeding and can be an important component of multimodal pain approach.[73]

Emergence delirium may be decreased with a single IV bolus dose of dexmedetomidine 0.5 ug/kg given 5 minutes before the end of surgery thus providing a smoother transition to the post anesthesia care unit.[74] A prospective study of 122 patients, age 2-10 years undergoing tonsillectomy with sevoflurane anesthesia received IV dexmedetomidine 2 ug/kg over 10 min followed by 0.7 ug/kg/hr and were compared to a group receiving IV fentanyl 1 ug/kg. The dexmedetomidine group needed less rescue analgesics with fentanyl, had a lower heart rate and systolic blood pressure and also required less morphine in their postoperative period. Severe emergence agitation on arrival to PACU was lower and the duration was shorter in the dexmedetomidine subjects.[75]

After completion of the procedure patients should be awake and be able to maintain their upper airway patency. Deep extubation is not recommended in patients with severe OSAS or those with comorbidities because they are at risk of persistent OSAS after surgery. Before extubation a nasal airway can be placed in patients with severe sleep apnea. The lateral decubitus or prone position can help relieve airway obstruction after extubation.

Postoperative intensive care unit admission is reserved for very severe OSAS, very young children, morbid obesity (BMI >40) and those with comorbidities that cannot be managed in a regular unit.[76] Asthma is also

associated with an increased risk of respiratory complications after adenotonsillectomy and these children may need a higher level of monitoring postoperatively.[77] Patients with mild to moderate obstructive disease (AHI <10) and no comorbidities can usually be discharged home the same day if they are greater than 3 years of age.

There have been fatalities reported in children with OSAS given oral codeine for pain management at home precipitating a recent boxed warning and contraindication released by the FDA recommending against use of codeine in children undergoing tonsillectomy. These children may be part of a group of extensive or ultra rapid metabolizers that have a greater production of potent morphine from its parent drug codeine. The genetic pattern occurs in 1-10% of individuals of European descent but up to 30% of North African descendants and must be considered with codeine use.[78] Given this data and the increased use of intravenous acetaminophen during the operative procedure, a safer drug to give in the PACU before discharge maybe oxycodone elixir (1 mg/ml preparation), 0.1 mg/kg up to a maximum dose of 5 mg rather than acetaminophen with codeine. This also avoids the problem of acetaminophen excess in the immediate postoperative period, although oxycodone is a drug that requires some metabolism to be effective. Other options for postoperative pain management may be oral liquid opioids not metabolized by CYP2D6 such as morphine or hydromorphine.

Although the respiratory distress index improves in children with severe sleep apnea and in obese children with OSAS after adenotonsillectomy, OSAS may not resolve in the majority of these children. In addition, enlarged lingual tonsils were found to contribute to persistent OSAS after adenotonsillectomy in children and also found to be more prevalent in patients with Down syndrome.[79] It is important to realize that these children may have increased anesthetic risk and need special care if they return for other surgeries.

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Chemical Dependency and Anesthesiology

John Tetzlaff, M.D. **Cleveland, Ohio**

The discovery of anesthesia and addiction to the drugs used to provide anesthesia have a common origin. Cocaine had a social use profile before its incidental discovery as a topical anesthetic. Experiments with injection of cocaine to anesthetize plexus and peripheral nerves led to addiction of early 20th century master surgeons, such as Halsted, who performed the experiments. (1) Early experimentation with ether, nitrous oxide and chloroform also caused psychological and even physical addiction. It is not surprising, therefore, that addiction to anesthetic drugs and anesthesiology remain linked and that addiction remains the most prevalent, serious occupational health risk associated with anesthesia. Because of the morbidity, much is known.

Scope of the Problem

Although addiction to anesthetic drugs has become a prominent issue for anesthesiology in the United States, this issue is neither new nor restricted to the USA. In an early report, Bruce (2) reported on the mortality and causes of death of anesthesiologists, noting lower death rates in most categories, except suicide, which was three times the rate for other physicians (1947-66). Lew (3) reported similar data (1954-76), with lower overall age-adjusted mortality, except for 6.2% suicide (2 times normal) and 6.9% "accidental". Although the suicide rate is higher in general for physicians (4), suicide in anesthesia providers is highly associated with addiction. (5) Ward (6) surveyed residency and nurse anesthesia programs for 10 years prior to 1982. With a 74% response rate, the incidence of addiction was 1% per year of giving anesthesia for the first five years. Gravenstein (7) reported the same 1% addiction rate with an alarming mortality of 7 providers out of 44 reported. The issue is also not restricted to the United States. Berry(8) survey 304 departments of anesthesia in the United Kingdom and Ireland and found cases in this interval (1990-99) in 39% of departments reporting (71.7% response rate) and drew the remarkable conclusion that one anesthesia provider per month in the United Kingdom was disabled by addiction. Weeks reported a comparably high incidence for Australia and New Zealand (51). The risk is not limited to physician anesthesiologists, with comparable or higher rates in CRNAs, with as high as 10% risk for a full career. (9)

Even though the issues are now well known and education/prevention steps are widely in use, the incidence has not seemed to change. Booth(10) surveyed 133 programs in 1997, achieved a 93% response rate, and reported 1.6% addiction rate in residents and 1.0% in faculty, despite 47% of respondents reporting increased education and steps to prevent diversion of controlled drugs. Collins(11) surveyed 176 programs (M.D. and D.O.), achieving a 66% response rate, with 80% of responding programs reporting at least one incident in the interval (1991-2001) with 19% reporting mortality. If anything, the mortality may actually be increasing, by comparison of the Collins (11) data for the 1990's with the 10% mortality reported by Spiegelman. (12) Warner reviewed the ABA database between 1975 and 2009 and found the incidence to be highest after 2003 with an overall incidence of 0.86% incidence at some time during training and a 7.3% mortality of those who demonstrated substance abuse disorder. (103)

Speculation about the Cause

While there will never be absolute proof, there is a consensus that a variety of issues combine to create a high risk of addiction. These include exposure to the drugs, familiarity with their pharmacology, access, stress and the uniquely addictive properties of anesthetic drugs. Prior addictive and high risk behaviors seem to be highly associated. Chemical experimentation in medial students has been reported (13) be 30-50%, and several reports have suggested that prior illicit drug use may motivate (consciously or unconsciously) the individual to choose anesthesia. (11, 14) In a large series, high risk behavior was found to be highly predictive of addiction. (15)

Occupational exposure seems to be a clear association. As previously mentioned, early experiments to create safe anesthesia techniques (nitrous oxide, ether, chloroform, cocaine) created victims of addiction in the investigators. The high incidence identified is even more remarkable when the early presentation of addiction is considered. In both physicians and CRNA, the incidence of addiction is highest during the first 5 years of giving anesthesia. (6, 16, 17, 18, 52) There is other suggestive evidence that the risk is giving anesthesia. Oral surgery residents in some maxillofacial residency programs receive extensive training (often from anesthesiologists) in giving anesthesia, and they report the same incidence of addiction proportionate to time in anesthesia with the same drug profile. (17) The

converse is equally true- physicians who do not practice anesthesia (internists) have a lower rate of addiction and suicide compared to an age and gender matched cohort of anesthesiologists [53].

Simply experiencing clinical anesthesia alone is too simple of an explanation for the risk of addiction. Gold has presented a provocative hypothesis that aerosol contact with fentanyl during opening of fentanyl ampoules[1] or from exhaled breath of patients[72] or contact with fentanyl or propofol from working surfaces within the operating room [77] may cause neurochemical changes in the brain that predispose some providers to become addicted [73]. They confirmed this hypothesis by detecting fentanyl and propofol in the air in several locations within active operating rooms [78]. The ASA Committee on Occupational Health has responded with the observation that exposure to fentanyl as a cause is preliminary data that should be further evaluated, citing a variety of methodological issues. [57] The neurochemistry of addiction is becoming well understood, with chemical changes in the reward centers leading to exaggerated need for drug acquisition, and exaggerated reward from experience with the drug.[89] Another possible explanation is a lower density of dopamine receptors in reward centers, resulting in less reward from natural reinforcers. [91, 92] The changes in the D-2 dopamine receptor are persistent or permanent and have the same molecular morphology as brain injury. [113] In adults with addiction to gambling, increased activity in the reward center in response to gambling prompts is detected by functional MRI, compared to controls [101]. Dopamine down-regulation has also been implicated in eating disorders, analogous to substance use disorder [114]. A molecular mechanism for the sensitization has been suggested by Kovacic, who reports that addictive substances have in common the ability to create reactive oxygen species (ROS) that result in electron transfer that activates brain reward centers [80]. Further work has established that metabolites of propofol and fentanyl create these ROS messengers [81].

Other elements of anesthesia practice that contribute to addiction are less objective but undisputed. The anesthesia provider is unique in organized medicine in providing "start-to-finish" administration of controlled substances. Even the most junior resident will obtain-fentanyl, draw it up, decide to inject, observe the effect, chart the intervention and handle the accounting of waste, often without any observed assistance. No other resident routinely has this experience or possesses these skills. New anesthesia providers also rapidly learn the clinical pharmacology of these substances by observation, reading and trial and error. This creates both the skill for self-medication, and the more ominous skill to achieve painless suicide. Self-medication may be an occupational hazard of the operating room related to stress and lack of positive reinforcement. New anesthesia providers get a disproportionate level of the work, their skill level is lower and as a result, their efficiency is low. And the operating room is rough on newcomers. These factors, combined with some natural curiosity about the drugs being used, create an unfortunate propensity for anesthesia newcomers to self-mediate. They know how, what to use, and the fallacy in the highly educated provider is that they can control the experience. Unfortunately, this initiates a cascade of use and addiction that accelerates at a very rapid rate. Gold [1] reports a case where a single experiment with intranasal accelerated to injection of 30mL/day of sufentanil within 30 days. In the context of high stress, reduced self-esteem and availability of synthetic opioid, Ward [18] states that control is gone after the first self-medication even though the individual doesn't know it. Farley [19] identifies other unique element of anesthesia practice, including a "chemical solution" to solving problems, and the isolated nature of anesthesia practice. Moleskin [20] further speculates that routine use of controlled substances minimizes the importance of tight accounting, desensitizing the individual to its relevance.

Other features may be triggering events for the subset of providers. Prior experience with substance abuse or high risk behavior has been previously identified. A prior history of psychiatric illness (contributory or coincident) can be contributory in the addicted anesthesia provider. [15, 16, 21] Personality disorders [74] and primary psychiatric diagnoses [75] are commonly found in addicted physicians, and self-medication may represent a response to these symptoms. [76] Burnout and depression are reported to be prevalent within anesthesiology, particularly among anesthesiology residents. [108] Depression is known to be associated with suicide, and although complicated, may be linked to self-medication and addiction [82]. There is strong evidence for a genetic susceptibility to addictive behavior, especially the transition from abuse to dependency.[88] Self-medication of psychiatric symptoms is a major cause of relapse of substance abuse disorder. [109]

Drugs Involved in Addiction for Anesthesiologists

From the substance abuse literature, the progression of substance (ETOH to marijuana to cocaine) is a common observation. Addiction within anesthesiology does not follow this pattern. Although the incidence of addiction to

drugs used in anesthesia is alarmingly high, the incidence of abuse of illicit drugs (alcoholism, THC, cocaine) is low. Addiction within anesthesia has always focused on anesthetic drugs. Prior to 1980, the drugs involved were meperidine, diazepam, and barbiturates.[22,23] After 1980, addiction has been heavily concentrated in the fentanyl family [6,10,17,19] Although parenteral fentanyl is the rule, severe addiction to oral fentanyl has been reported, although the victim was a nursing supervisor who lacked some of the parenteral administration skills.[24] Although rapid metabolism would seem to make parenteral remifentanil abuse seem unlikely, intranasal self-administration has been reported as the entry point to a fentanyl addiction [79]. Midazolam [17] and ketamine [25] have been reported in addiction cases, as has nitrous oxide[54] and potent inhalation agents, such as enflurane.[26] In a survey of academic departments, 22% reported at least one incident with an inhaled agent with less than half of the individuals involved entering rehabilitation, less than 30% return to practice, and a 26% mortality rate.[64] Propofol is the newest player on the scene with one case report [27] involving injection to unconsciousness up to 15 times per day. In another case report, propofol replaced a benzodiazepine because of superior sedative properties for the affected physician. [110] In a survey of academic anesthesiology programs from 1995-2005, Wischmeyer reported 18% of programs had a propofol abuse incident with 28% of the cases detected by death.[71] Repeated, prior exposure to propofol may be causative, with experience of the euphoria leading to intense craving and psychological dependence. [94, 95, 96]

The addiction potential with anesthetic drugs has been reviewed. Propofol has been tested in volunteers and found to have properties associated with addiction,[27] although the pharmacokinetics predict a difficult abuse pattern, requiring either pump infusion or frequent, intermittent injection. The addictive potential for other uncommon substance has been predicted based on the side effect profile, [28] including local anesthetics (dysphoria), cocaine (euphoria, stimulation), anticholinergics (psychotomimetic), antihistamines (sedation) and ephedrine (stimulant). Ketamine has an obvious role in those with prior psychotropic drug use, such as LCD, or PCP. [25, 29]

Detection

Self-reporting of serious addiction is uncommon. Direct observation of abuse and audits that confirm suspicion are the most common means of detection. Unfortunately, suicide, accidental death and coma combined are more common than self reporting.[19] Suicide during evaluation of possible addiction is a serious issue.[30] Intervention must be conducted carefully, with the goal of getting the suspected addict into a safe treatment facility, using progressively increasing motivators like reporting, termination, and as a last resort, police involvement. In one case, the cause of death was determined to be propofol by hair analysis where blood and urine toxicology were negative. [31] In cases where suspicion is high and urine toxicology is repeatedly negative, hair analysis has detected addiction to fentanyl, sufentanil, and alfentanil [55]. Detection of drugs with brief half-lives such as ketamine, midazolam and propofol are difficult or impossible in routine toxicology[27,32] and may require either observed abuse and rapid “for cause” screening, or hair analysis.[33,55] The fentanyl family is especially difficult to detect because of the brief plasma half-life and non-detection of metabolites.[24,34] A computer profile of drug use to detect outliers might be a better approach.[35] Epstein has prospectively applied this computer profile, and demonstrated that it detects diversion months before clinical detection, although its sensitivity needs to be refined before it becomes a first line tool, due to false positives. [87] Another electronic approach, using run charts comparing individual use against time to identify upward trends in individuals, also shows promise.[90] A promising opportunity for detection of is a urine assay for detection of the glucuronide metabolites of propofol, present in the urine for up to 3 days after exposure.

The urgency for detection of diversion of substances has never been low, but it has increased dramatically with the disclosure that individuals involved in diversion have used techniques that have resulted in injury to patients. Clusters of hepatitis infection have been traced to diversion practices of an infected health care provider [98]. Irresponsible handling of diverted substances and/or equipment presents a risk to all other health care workers [99]. The risk is particularly relevant given the variable level of prevention of diversion from institution to institution and state to state [100].

Re-entry

Addiction is a disease as well as a federally protected disability, as long as the addict remains in treatment. [67] Treatment only succeeds when evaluation reveals addiction and the victim is able to fully acknowledge their addiction. This is rarely (if ever) successful without in-patient treatment, graded re-entry with a contract, handling

of addictive substances by other providers, and random testing, including periodic hair samples. More controversial are the pharmacotherapeutic options, including naltrexone [111] and buprenorphrine. [112]

Even with the risk, a simple majority of providers will want to re-enter anesthesia. The outcome, however, is not always promising. In general physicians have a better outcome in rehabilitation from addiction [102] than non-physicians [36] even from opioid (prescription) abuse. [60] The California Physician Diversion Program's data suggests that this also applies to addiction involving anesthesiologists, although their definition of recovery may be very generous.[37] Some other data is in agreement,[38] however there is also evidence that re-entry is both ineffective and risky. Collins reports a 40% failure rate with re-entry of residents and 9% mortality. Re-entry for student nurse anesthetists has the same poor prognosis.[39] Merk reports 34% successful re-entry for residents with 13 having the first presentation of relapse as death.[40] Bryson[58] reported a graded re-entry of residents involving work in a simulation center for the first 12-15 months prior to re-entry. The value of this approach has been challenged [59] in light of the 60% relapse rate they report, and there remains a serious doubt that re-entry is ever the right choice for a resident [67]. The failure rate, the cost to the department with attempted re-entry, and the mortality rate led Berge [68], in an editorial in Anesthesiology, to advocate "one strike and you're out", a universal prohibition to re-entry. Oreskovich [69] and others responded to this strong position with circumstances where this would be excessive and highlighted the role of the highly effective state Physician Health Committees (PHC). It may be that the resident failure rate is related to the less universal role of PHC in the re-entry of residents.

Hedberg [41] has attempted to quantify the process by defining criteria that predict success and failure with re-entry. He has divided anesthesia providers in rehabilitation into three categories based on specific criteria, with category two needing delay and re-evaluation after one to two years and category three being individuals who should never practice anesthesia. Domino reports greatly increased risk of relapse when there is a coexisting psychiatric disorder, family history of substance abuse, or in those addicted to opioid, with the increase even greater if more than one of these risk factors is present[56]. Re-entry may actually oppose the process of recovery by re-exposing the addict to the visual, olfactory or physical cues to the emotions that triggered self-medication, and also may explain why delayed re-entry is required [65]. If re-entry is attempted, the focus should be on prevention of relapse [84]. There is even risk of relapse from subsequent required medical care, if exposure to triggering substances (opioids, propofol) is required for medical or surgical care. [93]

Prevention

There is universal agreement that mandatory education about the risk of substance abuse, stress and fatigue management should be a part of all anesthesia training programs at the entry point and regularly thereafter. There is also general agreement that this education process should continue beyond residency, although this is less universally applied. Despite evidence that the majority of training programs have increased their education programs, Booth [10] reports no change in the incidence of substance abuse. Previous reports of inadequate education [42] have created the education but not decreased the risk. Increased effort to prevent the diversion of controlled substances has also been instituted in a majority of programs [10, 43] including locked boxes, dispensing machines, video surveillance and satellite pharmacies. Some effect has been observed, including reduced controlled substance discrepancy. [20] Electronic data analysis can reveal average user profiles, and provide detection via outliers. [20, 35]

The subject of random drug testing is controversial [83]. The almost infinite number of ways to tamper with urine toxicology screening must be considered. [70, 86] The issue of false positives, even with the use of a medical review officer remains an administrative issue with intense consequences. [107] Although a promising avenue in the future, detection of anesthesia drugs in oral fluid is not possible at this time [85]. In responses to the survey of Booth, [10] a majority of chairs favored random testing, although only two programs outside the military have instituted such a program. Fitzsimons [61] presents the first five years of one of these programs designed to prevent addiction which includes a random testing element, and reports no addicted providers detected. The Department of Transportation (DOT) has had a random screening program for almost two decades for commercial drivers, railroad and airline pilots. Industry has followed, with more than 90% of companies with more than 5000 employees having some kind of testing. [44] Random testing programs have been shown to reduce positives [45] and save health care dollars. Mike Scott, previous council to the ASA, has written a review of random testing, [46] in which he identifies the AMA endorsement of "for cause" testing and discusses the unresolved legal issues with random testing. Although random testing is prohibited in 12 states, there are exceptions for industry involved in safety. Concerns by the AMA are

expressed in an editorial which discusses privacy, handling of false positives, confidential records and the approaches to randomization.[47] A more recent editorial in by Pham in JAMA advocated random urine testing for all physicians as a means of ensuring patient safety.[104] Although disputed in responding letters to the editor of JAMA based on lack of supporting evidence [105,106] the same sentiment was echoed in an editorial in the New York Times ("Why Aren't Doctors Drug Tested?"- March 12, 2014) which advocated universal drug testing for all health care workers with contact to controlled substances. DOT rules have created the need for the role of a Medical Review Officer, a physician with specific training to handle the initially positive screen.[48] All recovering physicians are subject to random screening during recovery and any failure or absence requires action.[49] Collins [11] data reveals a slightly higher rate of pre-employment screening (16%) and pre-employment toxicology screening. Based on the kind of data in Men's Health [50] ("the Junkie in the OR") and two recent cases that made headline news in the press on the East Coast, the lay public may begin to demand random screening. It is clear that detection during residency training is a responsibility of the residency program.[62] Failure to report provider impairment may incur legal liability for the anesthesia department, the hospital or anesthesia groups who know.[63] Regardless of the legal risk, protocols for handling of impairment and substance abuse should be present in every department.[66]

Conclusion

Substance abuse is the most serious occupational safety hazard for anesthesiology. Causing devastating consequences to the career, morbidity, personal stress and death, it is a high attractive target for prevention. The nature of anesthesia (working alone, production pressure, isolation) and the handling of highly addictive drugs are contributors. Up to 1% per year of residents may become addicted. The mortality rate of relapse may approach 9%. Prevention by education, tight control of controlled substance use, profiling for outliers and possibly random urine toxicology may be needed to arrest this serious hazard of providing anesthesia.

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Failed laryngoscopy—what now?

Richard M. Cooper, BSc, MSc, M.D., FRCPC. **Toronto/ON Canada**

What do we mean by failed laryngoscopy?

A "difficult airway" includes problems encountered performing one or more of 1) laryngoscopy, 2) intubation, 3) ventilation by facemask or supraglottic device or 4) a need for an emergent surgical airway. Difficulty may also be encountered in re-establishing an airway following extubation.

Successful laryngoscopy and intubation may be related but they are not interchangeable. As anesthesiologists, we perform laryngoscopy to enable visualized placement of an endotracheal tube. *If we fail to visualize the larynx, then laryngoscopy has failed.* Blind placement of an endotracheal tube may be a successful intubation but it should be understood to have been a failed laryngoscopy. On the other hand, laryngoscopy may provide a good laryngeal view but intubation can't be achieved. Inherent in the distinction between successful laryngoscopy and intubation is the fact that blind intubation is more likely to fail or be injurious than a visually controlled intubation. The current ASA Airway Task Force Practice Guidelines regards an airway event as difficult when a conventionally trained anesthesiologist requires "multiple attempts."[2]

How often does failed laryngoscopy occur?

We are advised to conduct a thorough bedside airway evaluation prior to initiating airway management although these guidelines also state that there is insufficient evidence supporting the value of this assessment in predicting difficulty.[2] Often forgotten is that these bedside predictors for laryngoscopy were developed specifically for direct laryngoscopy (DL) and may not apply to other techniques. Indeed, many studies fail to even describe the device employed. A meta-analysis of 35 studies involving 50,760 adults with seemingly normal airway anatomy found that the commonly performed bedside tests had only moderate predictive value when performing DL and a Cormack-Lehane grade III view ("failed laryngoscopy") was seen in 5.8% of patients.[3] Even more worrisome is a Danish study that looked at a national database of 188,064 adults intubated for anesthesia. Anesthesiologists were required to indicate whether difficulty was anticipated (Y/N). They found that 93% of "difficult intubations" performed by DL were unanticipated, requiring more than 2 attempts, rescue with an alternative device or failing outright.[4]

Both the prediction of airway difficulty and how easily it is managed does not really lend itself to a binary evaluation and is probably better described along a difficulty continuum.[5] An intubation difficulty scale (IDS) looks at parameters including the laryngeal view, number of attempts, number of operators, alternative techniques and the amount of applied force. Minor airway difficulty was encountered in 37% of routine anesthetics; moderate intubation difficulty (IDS>5) was encountered in nearly 8% of 1171 consecutively anesthetized patients.[6] Furthermore, moderate difficulty was encountered more than twice as frequently when intubation was attempted outside of the operating room.[7,8] In the operating room, three or more attempts using DL have been required in about 1-2% of patients.[9]

What do we do when DL fails?

DL frequently fails because of our inability to achieve a direct line of sight (see figure 1). This may be dealt with in several ways: repeated attempts[10] with increasing force, positional adjustments, adjuncts (e.g. stylets, tracheal introducers), external laryngeal manipulation, a call for assistance, the use of alternative devices (e.g. video laryngoscopes, optical stylets, flexible endoscopy), reversion to face mask or supraglottic ventilation, waking the patient or performance of a surgical airway.

There is evidence that multiple intubation attempts incur incremental risk. Mort has demonstrated that outside the operation room more than two laryngoscopy attempts significantly increased the risk of SpO_2 <70% 14-fold, esophageal intubation 6-fold, regurgitation 7-fold and cardiac arrest 7-fold.[11] In the emergency department, the

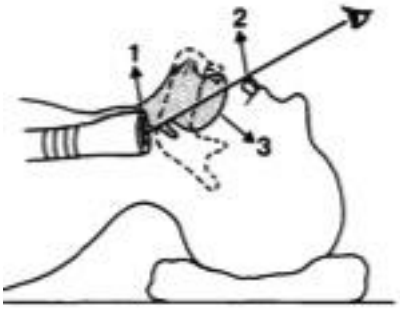

Figure 1 *(from Cormack and Lehane 1984, with permission of the publisher)*

number of adverse events increased with multiple attempts. From the first to the fourth intubation attempt the percentage of patients suffering adverse events increased from 14%, 47%, 64% and 71% respectively.[12]

More than one attempt at tracheal intubation was a significant predictor of one or more adverse events (adjusted OR-7.52, CI 5.86-9.63). Although these studies were performed outside the operating room, they likely apply to critically ill patients in any location and may be relevant to healthy surgical patients as well. They suggest that we should minimize the number of required intubation attempts and strive to achieve first pass success (FPS).[8,13,14]

It is easier to prevent desaturation than to correct it. We should make every effort to optimize pre-oxygenation with a tight-fitting face mask or high-flow nasal cannula.[15]

"Never fail to prepare for failure"[16]

An airway manager's overall objective is maintaining oxygenation. This can be achieved by face mask, supraglottic airway, tracheal tube or an emergent surgical airway. Repetition of a technique that had previously failed should only be done if there is a compelling reason to believe that it will likely succeed. Otherwise, we are wasting precious time, squandering an opportunity and potentially converted a can't intubate situation into a can't intubate/can't oxygenate (CICO).

Our first intubation attempt should be optimal using a familiar device, proper patient and operator positioning, an appropriate tracheal tube (with a pre-inserted or immediately available stylet or tracheal tube introducer) and suitable drugs. If in spite of this, we fail to view the larynx, we should reassess the situation. We might now know that DL will not succeed—multiple attempts are not only unnecessary but possibly harmful. Oxygenation can be more objectively assessed than the adequacy of ventilation; believe the oximeter since ventilation is frequently misjudged in stressful circumstances.

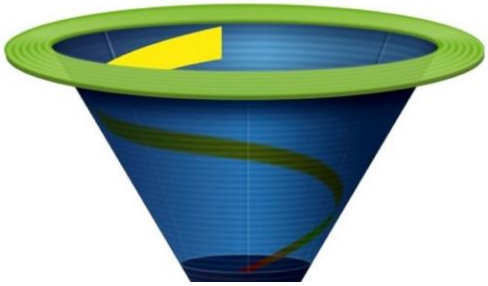

Figure 2 Vortex Airway Approach©--reproduced with permission from Nicholas Chrimes[1]

The ASA Difficult Airway Algorithm may be educationally helpful in formulating a strategy, but it is complex and may produce cognitive overload in an emergency. Furthermore, these and other guidelines represent a concerted effort to be evidence-based but high-quality evidence is often lacking. For the most part, they are a consensus of expert opinions.[9,17-20] They were not intended to dictate practice but rather to guide the decisions made by thoughtful care providers. Perhaps a more appropriate device is a "cognitive aid" such as the Vortex Airway which does not compete with existing algorithms but rather serves as a checklist that can be posted and read aloud when airway problems are

encountered (Figure 3).[1] This tool, or one like it, will ensure that details have not been overlooked. Perhaps even more useful, is the simplified construct of a "vortex" wherein critical decisions must be made with increasing rapidity as oxygenation deteriorates (Figure 2). In the "green zone," there is time to consider moving between a face mask, supraglottic airway or limited attempts at laryngoscopy with adjustments in position, adjuncts, a different laryngoscope blade, the addition of a stylet, external laryngeal manipulation etc. In the "blue zone," failing oxygenation makes immediate rescue essential. As the blue intensifies, the amount of time between transitional maneuvers is reduced. Can't intubate/can't oxygenate (CICO, pronounced KY-KO) should be recognized, declared and the entire airway team mobilized to prepare for a surgical airway ("CICO Rescue"), even if ultimately not required. A delay in recognizing such a situation may have a catastrophic outcome.

Failed laryngoscopy with adequate oxygenation

If oxygenation is adequate, there is time to consider other options, which may include the use of a supraglottic airway as a definitive airway or a conduit for intubation, use of an alternative device, waking the patient and postponing surgery or managing the airway awake.[2,9,18] It is best to declare the proposed strategy aloud. This prepares the team and maximizes their value to the airway manager. A difficult airway cart ensures that the required equipment is immediately available. This can also serve as a cognitive aid presenting options that may not be obvious in times of stress. Unfamiliar devices are of limited value and may actually be harmful under these circumstances. The time to prepare for airway emergencies and become familiar with alternative techniques is when a patient's life is not dependent upon successful performance. Finally, managing a failing airway is not about the operator; it's about the patient. People who arrive to help are not there to compete; they need to be empowered to make suggestions and assist.

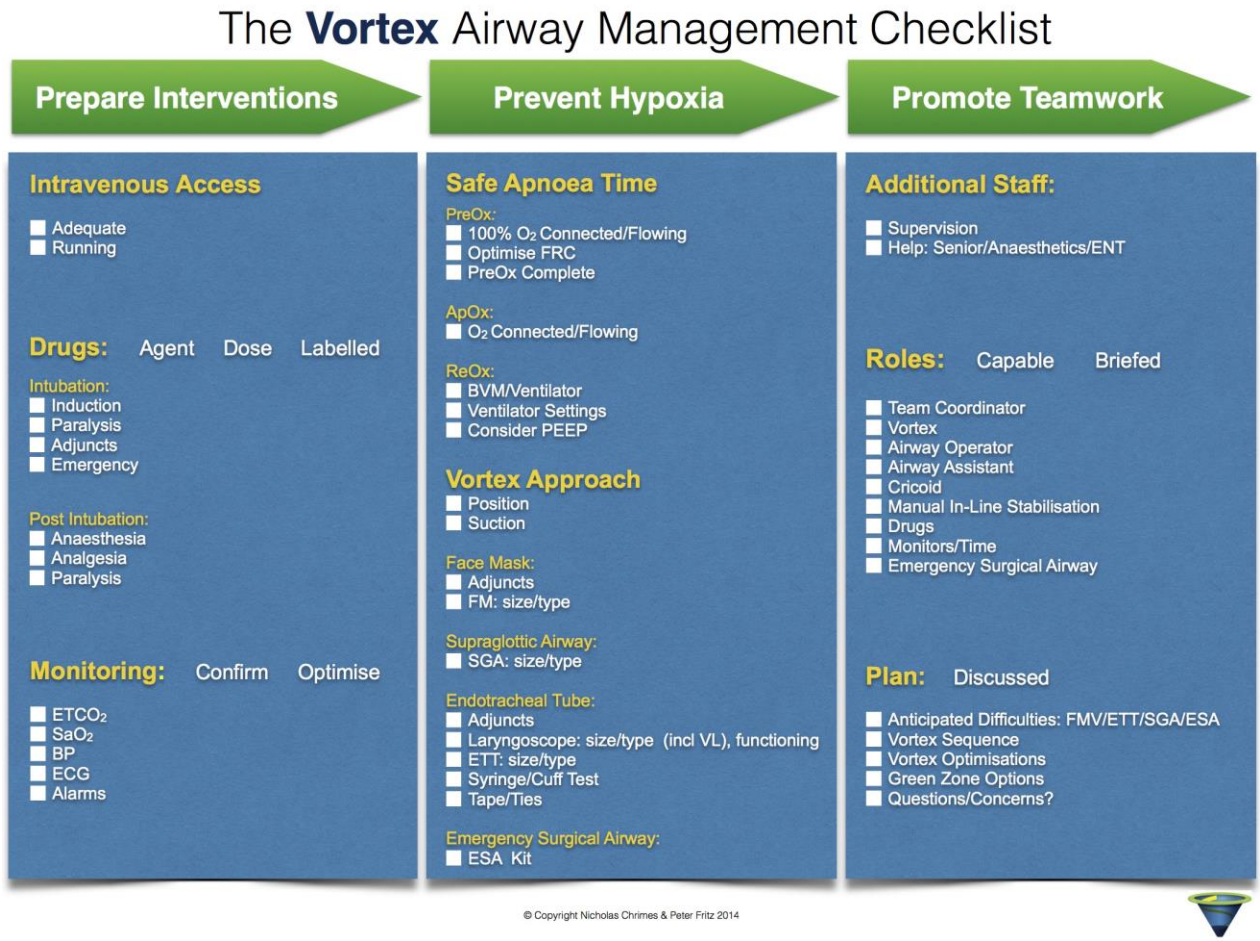

Figure 3 *Vortex Airway Approach--Reproduced with permission from Nicholas Chrimes*[1]

Oxygenation and protection from aspiration are always of paramount importance. If no laryngeal view is obtained, simple adjustments may be considered, but the probability of success should be weighed against the time required to perform them. For example, external laryngeal pressure[21] (or BURP) and/or head elevation[22] can be considered, taking little time. A blade change may be considered though this is likely to be helpful in limited circumstances. A tracheal tube introducer (aka "bougie") can be attempted if its coudé tip can be visually positioned beneath the epiglottis and directed through the vocal cords.[9] But this remains a blind procedure and may be difficult to justify if oxygenation is stable and alternative equipment and expertise exists.

The availability of video laryngoscopy and optical stylets has dramatically changed airway management. Because these devices are not reliant upon a line-of-sight (figure 1), when positioned at the tongue base, they often provide an excellent glottic view, converting a blind procedure into one that can be visually controlled. But the techniques used for direct and indirect (video) laryngoscopy differ.[23] Furthermore, not all video laryngoscopies are alike and the non-channeled devices in particular, require the additional skill of delivering the tracheal tube to the larynx.[24] Regular use is important to acquire familiarity and maintain skill with the devices you are likely to encounter. If these devices are reserved for rescue purposes, they are more likely to fail because of insufficient familiarity, limited time and situational stress. When oxygenation can be maintained and intubation is deemed appropriate, efforts should be made to perform this under visual guidance.[18]

Aziz and co-workers examined the electronic anesthetic records at two centers and found 2,004 instances wherein the GlideScope Video Laryngoscope (GVL, Verathon Medical, Bothell WA) had been used. This represented 2.8% of intubations attempted, most of these patients having features predictive of a difficult DL. Of particular relevance to this discussion is the subset of patients in whom the GVL was used after DL had failed. This consisted of 239 patients. The success rate for a rescue was high but it differed at the two centers: 143/148 vs. 81/91. At the center with the higher success rate, the providers had performed a median of 19 GVL-assisted intubations compared with 6 at the other center.[25] Beyond proving its value in the rescue of failed DL, this study demonstrated that performance improves with experience. Numerous studies in a variety of settings, including emergency departments, critical care and obstetrical units have demonstrated the effectiveness of various VL in patients predicted to be difficult DL.[26-34]

A retrospective observational study involving seven American academic centers looked at rescue attempts after nearly 350,000 direct laryngoscopies between 2004-2013.[35] They found that video laryngoscopy was increasingly relied upon (1,032) and had the highest success rate (92%) compared with a SGA conduit (82 attempts), flexible bronchoscopy (170), lighted stylet (128) and optical stylet (9). The choice of video laryngoscopy increased from about 29% to 83% during the study period while all the other techniques declined.

The CAFG Guidelines concluded that "incremental risk must be assumed with each failed attempt such that a second or third tracheal intubation attempt should only occur if a different tactic is used with a reasonable expectation of success. Proceeding with more than three attempts at tracheal intubation requires compelling justification."[9] The Difficult Airway Society (DAS) Guidelines recommend a maximum of three attempts, a fourth being acceptable if undertaken by a more experienced person.[18]

Although exacting science may not support a specific limit on the number of attempts, it sets the goal posts, increasing the likelihood that efforts will not be wasted with ineffective methods that may cause incremental risk to the patient. If tracheal intubation cannot be achieved within three attempts, but oxygenation is adequate, the choices are to 1) awaken the patient, 2) continue anesthesia with a facemask or SGA, 3) call for help bringing additional equipment and assistance or 4) when surgery cannot be deferred and alternative strategies are unlikely to succeed, to proceed with a surgical airway despite the adequate oxygenation.[2,9]

Failed intubation with deteriorating oxygenation

Clinicians may fail to appreciate the inadequacy of ventilation but failing oxygenation can be objectively measured by oximetry. However, the shape of the oxy-hemoglobin dissociation curve means that oxygen reserves may be significantly depleted by the time the SpO_2 declines, and since deterioration may be precipitous, the time required to remedy the situation may be insufficient to prevent serious patient harm. Non-reassuring oxygenation implies that the situation is worsening mandating prompt action: 1) recognition, 2) declaration, 3) a call for help and 3) preparation for CICO Rescue (emergency surgical airway). It may seem like one is burning bridges however if intubation and oxygenation are failing (and waking the patient is not an option) full neuromuscular blockade should be ensured to optimize laryngoscopy, ventilation and a CICO rescue if required.[18]

Rapid recovery of spontaneous ventilation has become more feasible with ultra-short acting narcotics and Sugammadex. The value of the latter may be limited by delays in recognizing and declaring CICO, in obtaining and preparing the drug, pre-existing or induced airway obstruction as a result of "multiple" laryngoscopy attempts. These may prevent adequate re-oxygenation despite a resumption of spontaneous respiratory efforts.[36]

If resources permit, an additional attempt to place a SGA may be made if it does not delay preparations for surgical access. If oxygenation and ventilation can be re-established with a SGA, a medical emergency may have been averted and a thoughtful approach to the next step can be made. This might include a wake-up of the patient, persistence with the SGA or use of the SGA as a conduit for tracheal intubation. The latter approach should be part of the airway armamentarium of all airway managers and practiced in non-urgent situations.[37]

The method chosen to achieve surgical access has been widely debated but most anesthesiologists agree that the site is not a matter for debate—a cricothyroidotomy can be performed more quickly than a tracheotomy, with less risk of vascular injury.[38] The NAP4 report demonstrated that anesthesiologists in the UK performed this task poorly.[16]

Indeed, 58 of 133 serious complications of airway management involved an attempted emergent surgical airway with a failure rate of nearly 60%. The cricothyroid membrane is frequently incorrectly identified by palpation, particularly in females and obese patients.[39] If the space is incorrectly identified, positive pressure ventilation or jet ventilation will quickly result in barotrauma, obscuring the landmarks and compromising subsequent attempts. The barotrauma may itself be fatal. The cricothyroid membrane can be more accurately identified by ultrasound if time permits and the operator is experienced.[38] This argues for practicing the technique electively, when an ultrasound is available; when awake intubation is planned, the site can be punctured to instill local anesthesia and the correct location can be visually confirmed.

Others would say that the above argues for an alternative technique employing a scalpel to incise the skin and cricothyroid membrane, either a finger or bougie to enter the trachea and advancement of a tracheal tube over the bougie. There has been limited evidence that this method is the fastest, safest and most preferred technique[40] and the DAS has recommended this approach to achieve a CICO rescue or emergent front of neck access.[18]

When difficulties have been encountered, it is our responsibility to ensure that we communicate with those providing the subsequent care to minimize the risk of recurrence. This includes a thoughtful approach to the timing and method of extubation, one that maximizes the probability of safe reintubation if extubation should fail.[41] Ideally, detailed clinically relevant information should be accessible 24/7 from anywhere, even when the patient is insufficiently informed or unable to communicate. This can be achieved by explaining to the patient and family the importance of transmitting the information and promoting registration in an accessible database such as MedicAlert.[42]

Despite our focus on management of the failed airway, we have actually made great strides. Advanced Airway Management is emerging as a subspecialty with fellowships and relevant societies around the world. The first World Airway Management Meeting took place in Dublin in November 2015 and a follow-up conference is planned for Amsterdam in 2019. New pre-oxygenation strategies have been shown to extend tolerance of apnea;[43] there has been a proliferation of supraglottic airways providing more effective ventilation and better protection from aspiration; video laryngoscopes are widely available and often provide good laryngeal exposure when DL fails. Remote monitoring, mentoring and clinical documentation will potentially improve clinical outcomes.[44-46] Better selection of patients requiring awake intubation has been demonstrated by an preoperative endoscopic airway assessment.[47] This author is of the *opinion* that video laryngoscopy will emerge as the standard of care for intubation, at least in more prosperous regions. But it is not suitable for every situation and over-reliance on a single method will undoubtedly lead to a decline in our performance with other essential tools. We must practice with a range of devices, utilizing them whenever possible to ensure that we acquire and maintain the required skills to provide safe care.

Key points

- The goal of airway management is the optimization of oxygenation and protection from aspiration.
- The airway should be assessed and whenever possible, previous records consulted in an effort to anticipate airway difficulties. Bedside assessment is at best moderately sensitive and specific. These apply specifically to DL and have limited relevance when alternative techniques are used.
- DL frequently fails to reveal the larynx. Simple maneuvers such as external laryngeal pressure, head lift or use of a tracheal introducer may be tried.
    - Multiple attempts incur incremental risk and should only be made if there is a reasonable expectation of success.
    - A limit on the total number of permitted attempts increases the likelihood that unhelpful and possibly harmful efforts will be reduced or eliminated.
    - Failed laryngoscopy can often be rescued by indirect/video laryngoscopy in practiced hands.
    - Oxygenation is a more objective management outcome than the adequacy of ventilation.
    - Insertion of a supraglottic airway may restore ventilation/oxygenation but this may be compromised by multiple intubation attempts.
    - A well-seated supraglottic airway may function as an adequate airway or serve as a conduit for endoscopic-assisted intubation.

    - When failed laryngoscopy is encountered, the choices include a wake-up, ventilation by facemask or supraglottic airway, an alternative device and a call for help.
- When failed laryngoscopy and non-reassuring oxygenation are encountered, time is limited. A cognitive aid may reveal overlooked opportunities.
    - Call for help and a difficult airway cart.
    - Ensure adequate neuromuscular blockade to facilitate both ventilation and laryngoscopy.
    - A single attempt at insertion of a supraglottic airway is appropriate.
    - Quickly consider whether Sugammadex is a viable option
    - Preparation must be made for CICO Rescue.
- Extubation is elective. It must be thoughtfully carried out to avert a recurrence of the initial difficulties and maximize the probability of safe reintubation should it be required.[41]
- Communicate with subsequent care providers and encourage enrollment in a difficult airway registry

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Transfusion Therapy: Optimal Use of Blood Products

Stephen Surgenor, M.D. **Lebanon, New Hampshire**

Introduction

Despite decades of effort, transfusion therapy practice remains suboptimal. This review will examine the risks and benefits of red blood cell (RBC), platelet, and fresh frozen plasma (FFP) transfusions, as well as strategies to optimize transfusion practice for each of these components. The American Association of Blood Bankers 2011 Nationwide Blood Collection and Utilization Survey Report describes the current status of blood utilization in the United States. Key findings include that for the first time in two decades the annual number of transfusions has decreased, and that collection of autologous and directed blood is decreasing and now represents less than 2 percent of total donation. In addition, the use of leukocyte reduction continues to increase and now 80 percent of RBC units are treated. Figure 1 describes the collection and transfusion of blood nationally.

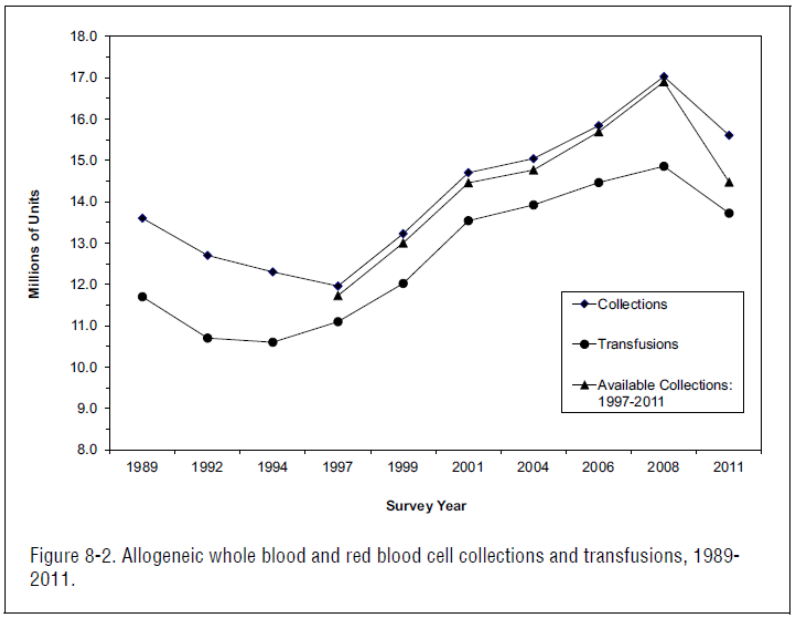

Figure 8-2. Allogeneic whole blood and red blood cell collections and transfusions, 1989-2011.

Figure 1. Allogeneic whole blood and red blood cell collections and transfusions: 1989 – 2008.
Source: American Association of Blood Bankers 2009 Nationwide Blood Collection and Utilization Survey Report.

Variation in Transfusion Practice

Tremendous variation in the indications for and timing of transfusions exists. Large variations in the indications for and timing of RBC transfusion have been documented for many years among coronary artery bypass graft (CABG) surgery patients[1] [2]. Importantly, this variation is not explained by patient or surgical variables, but rather by differences in provider and institutional preferences[3]. More recently, another observational study demonstrates that variation continues across institutions in Canada despite new knowledge about the benefits and risks of RBC transfusions[4]. Such variation is not limited to just RBC transfusions. Similar observations have been made for use of platelets and plasma during CABG surgery in Veterans Administration hospitals[5]. The presence of significant variation in transfusion rates implies that the best practice has yet to be identified, and that indications for transfusions are not consistent among providers.

Guidelines

This variation persists despite the availability of practice guidelines. One of the oldest guidelines for RBC transfusion is the "10/30" rule which originated from comments made by Adams and Lundy in 1942[6]. Several RBC transfusion guidelines have been published based on best available evidence by the National Institute of Health (1988), the American College of Physicians (1992), the Blood Management Practice Guidelines Conference (1995), as well as the American Society of Anesthesiologists. Most recently, a comprehensive guideline has been developed

by the Society of Cardiovascular Anesthesiologists for the cardiac surgery population[7]. There has been less activity to develop guidelines for platelet and plasma therapies; the only one was developed by the College of American Pathologists in 1994[8]. The American Society of Clinical Oncology has developed guidelines for platelet therapy among the oncology population, which are not easily generalized to either peri-operative or critically ill patients[9].

While medical guidelines are believed to be an efficacious method to improve medical care, they have been relatively ineffective in reducing unwarranted transfusions for several reasons. Specific to RBC transfusion, one prescribed trigger is not appropriate for all patients and clinical settings, because a consistent physiologic deterioration in is not observed among all patients at the same hemoglobin level. Second many physicians remain unaware of available transfusion guidelines.

This past year, Dartmouth Hitchcock Health system implemented a transfusion decision support tool in our electronic health record that is based on the current evidence yet allows clinicians flexibility to use blood for appropriate indications. The results of this effort are presented in Figures 2 & 3. This type of approach likely generalizable to other institutions, and represents one approach to effectively implement evidence based medicine in general, but specifically for transfusion medicine as well.

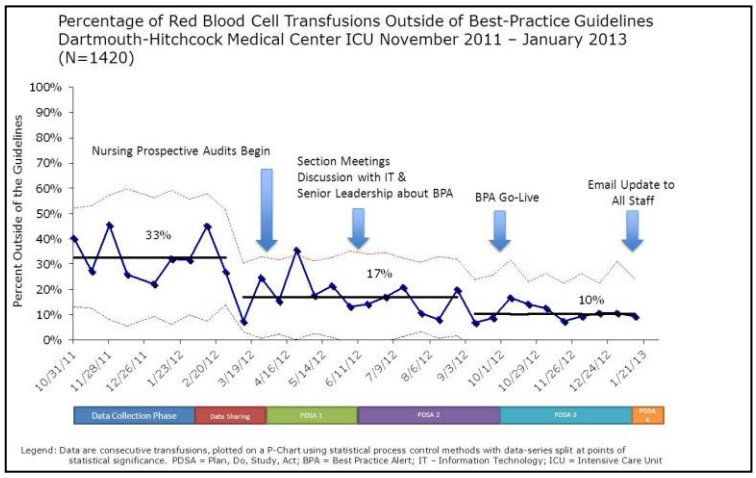

Figure 2 Results of an Electronic Health Record Transfusion Decision Support Tool.
Source: Unpublished Data from Dartmouth Hitchcock Health

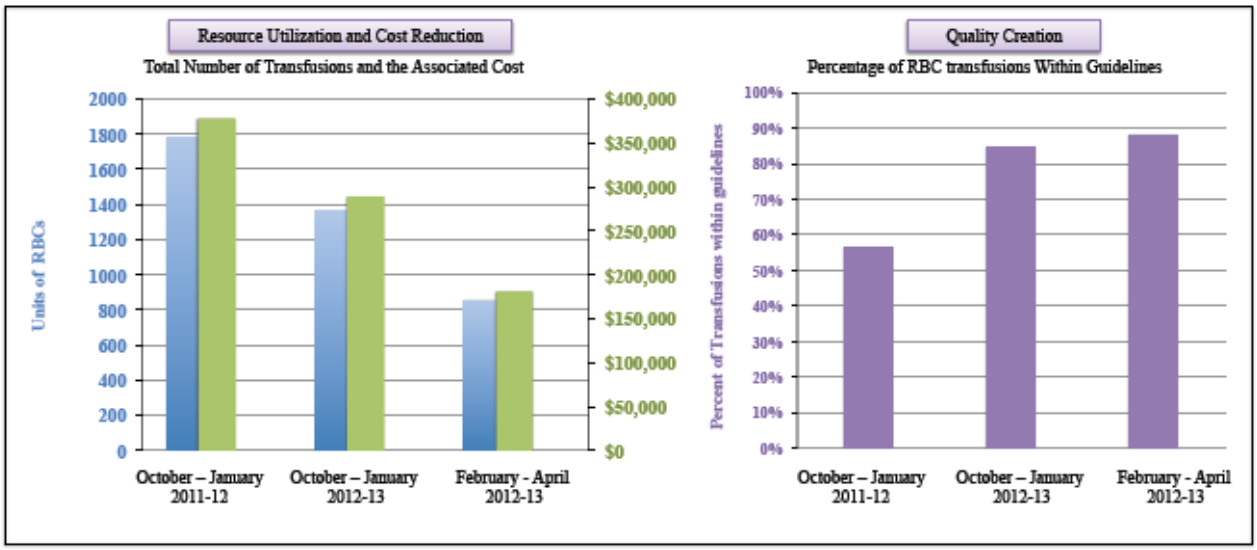

Figure 3 Results of an Electronic Health Record Transfusion Decision Support Tool.
Source: Unpublished Data from Dartmouth Hitchcock Health

Red Blood Cell Transfusions

Risks of Anemia

There are numerous reports of severe anemia being well tolerated in healthy subjects. Acute normovolemic hemodilutional anemia has been safely performed with animal models with dogs and baboons, as well as with human subjects with and without surgery. Data from patients who decline RBC transfusion for religious reasons suggests that mortality is more related to substantial blood loss than a low preoperative hematocrit per se. Importantly this effect was significantly more pronounced among patients with cardiovascular disease[10].

Studies from several prospective observational cardiac surgical databases have reported associations of hemodilutional anemia during cardiopulmonary bypass (CPB) with increased risk of renal failure, stroke, and mortality during coronary artery bypass graft (CABG) surgery. Plausible explanations for these observations include direct injury as a result of exposure to hemodilutional anemia or alternatively that these associations a a marker for another unmeasured process. One such process could be exposure to intra-operative RBC transfusions administered as treatment for anemia.

A report by the Northern New England Cardiovascular Disease Study Group observed that among patients managed without intra-operative RBC transfusion, exposure to hemodilutional anemia during CPB was associated with Low Output Failure (increased need for prolonged inotropes, post-CPB intra-aortic balloon pumps, and return to CPB after initial separation) (Figure 4)[11]. These observations support the concept that intraoperative anemia reduces the oxygen supply available to the tissues to adequately meet demand, leading to ischemic tissue injury and subsequent adverse outcomes.

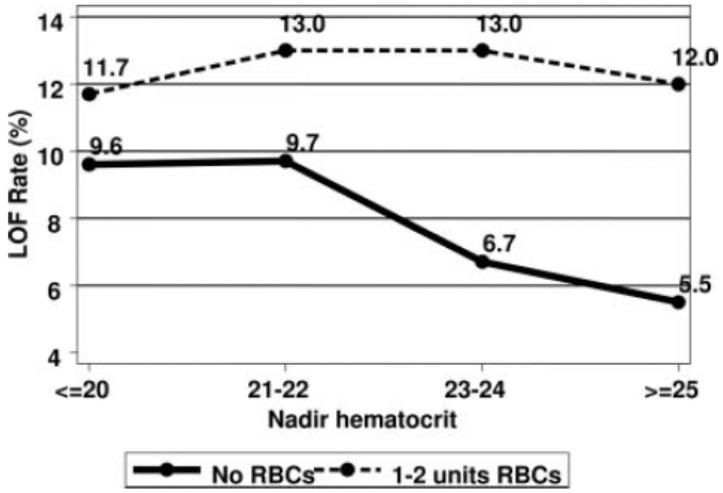

Figure 4. Crude risk of Low Output Failure by quartiles of lowest hematocrit during cardiopulmonary bypass stratified by RBC transfusion.

Benefits of RBC Transfusion to treat Anemia

The long standing belief for RBC transfusion is that giving back blood will reverse the ill effects of anemia. We now have three prospective trials comparing liberal and restrictive transfusion strategies among critically ill and peri-operative patients.

The first prospective trial of RBC transfusion therapy in critically ill patients without active bleeding was published in 1999[12]. The Canadian Transfusion Requirements in Critical Care, or TRICC trial, evaluated a restrictive strategy of maintaining hemoglobin between 7 and 9 g/dL versus a liberal strategy of maintaining hemoglobin between 10 and 12 g/dL. Inclusion criteria included anemic euvolemic patients who were not actively bleeding. Patients with chronic anemia of following cardiac surgery were excluded, and a large number of patients with significant coronary artery disease were not enrolled in the study at the discretion of the attending physician. This study showed that the restrictive strategy was "at least as effective as and possibly superior to a liberal transfusion strategy." Furthermore, subgroup analysis showed an association of improved 30 day survival in

patients younger than 55 years old or those with APACHE II scores lower than 20 managed with the restrictive strategy.

A more recent prospective trial of RBC transfusion during cardiac surgery was completed in Brazil[13]. Among 500 patients undergoing cardiac surgery with CPB, a restrictive transfusion strategy of tolerating anemia to a hematocrit of 24% was just as efficacious as a more liberal goal of maintaining hematocrit above 30%. The rate of RBC transfusion was 78 percent vs. 47 percent in the liberal versus restrictive groups. These finding are consistent with the TRICC trial conclusions.

Finally there is a prospective trial of liberal (greater than 10 g/dL) vs. restrictive (less than 8.0 g/dL) strategies among high risk patients after hip surgery[14]. Similar to the previously mentioned trials, there was no outcome benefit, as measured by death or inability to walk without assistance, to patients from a more liberal approach to transfusion. Nearly 97 percent of patients in the liberal group were transfused withRBCs. In the restrictive group, far less blood was administered, and only 40 percent of these patients were exposed to RBC transfusions.

There is one other randomized trial that provides some evidence regarding the role of RBC transfusion as part of early goal directed fluid therapy for treatment of sepsis or septic shock. Rivers et al. randomized septic patients to either standard resuscitation or an explicit goal-directed protocol[15]. RBC transfusions were indicated in the goal-directed protocol to maintain central venous oxygen saturation greater than 70 percent, if the hematocrit was less than 30 percent. Patients in the early goal directed group experienced superior hospital, 28-day, and 60 day mortality compared to patients managed with standard resuscitation. Because there were multiple interventions used in this protocol, it is not possible to separate the relative importance of RBC transfusion to the survival benefit.

Risks of RBC Transfusion

During the 1990s, the risks of RBC transfusion seemed to be well characterized. For example, there are well defined risks of viral transmission for cytomegalovirus, hepatitis C, hepatitis B, HIV and HTLV via transfusions[16]. Currently, for these viral risks, sophisticated patient screening, combined with laboratory detection methods have become quite effective. As a result, the risks for these viral transmissions have decreased dramatically over time (Figure 5). Transfusion has been estimated to be as safe as anesthetizing ASA I patients[17] . However, screening tests are costly, and contribute to the rising costs of blood therapy. There are emerging infectious risks that will require attention going forward, including Chagas disease, West Nile virus, Malaria, and Creutzfeldt-Jakob disease.

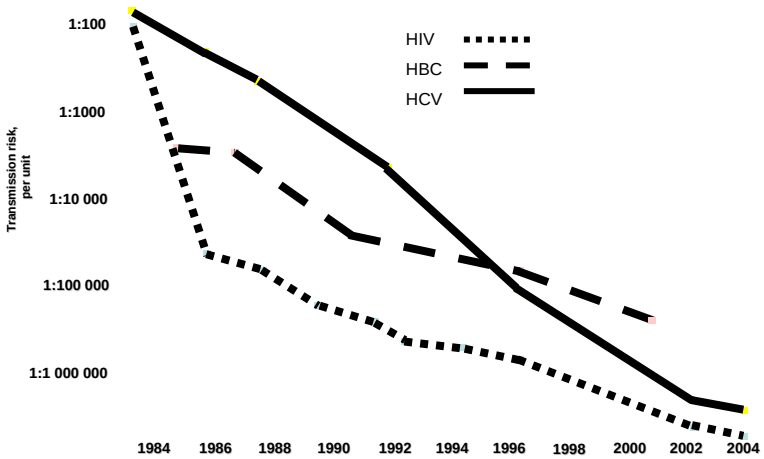

Figure 5. Evolution of Viral Risks Related to Transfusion over Time.

For current management of peri-operative or critically ill patient, the risk of viral infections is not among the major concerns. One issue that is of more consequence for the critically ill patient is the accumulating evidence that blood transfusion may have profound negative effects on the immune system. Clearly in an environment like the operating room or the intensive care units, where much of the morbidity and mortality is directly related to infection, if blood transfusion does in fact increase the risk for infection it is of major concern. In the late 1970's, it

was observed that renal transplant outcome was improved among patients receiving blood transfusions before the transplant surgery. There have been a large number of observational studies regarding the association of RBC transfusions with infection, immunosuppression, and mortality.

Several studies have suggested that exposure to RBC transfusion increases the risk of postoperative infection. Taylor et al recently observed that patients in a medical-surgical combined ICU experienced nearly a ten percent increased risk of nosocomial infection with each unit of transfused RBCs[18]. Chelemer et al made similar observations among patients undergoing CABG surgery[19]. There is also observational data that suggest decreased long-term survival after exposure to RBC transfusion during CABG surgery[20].

Other studies support the concept that transfusions induce immunomodulation in recipients. Fransen et al observed that intra-operative allogeneic blood transfusions were associated with increased concentrations of inflammatory mediators as well as increased postoperative morbidity[21] . Moore et al. reported the results of a prospective cohort study of trauma patients[22]. They found that there was a dose response relationship between early blood transfusion and later development of multiple organ failure. This was independent of other measures of shock. The mechanism for these associations remains unclear, but mediation by allogeneic white blood cells is the most likely etiology. These donor white blood cells may directly impact the recipient's immune function, or cause the release of mediators of immunomodulation into the stored RBC unit[23].

There are also observational data that suggest an association of RBC transfusions and increased risk of acute respiratory distress syndrome[24]. This observation is of interest when considered together with transfusion related acute lung injury (TRALI). TRALI is a non-specific constellation of dyspnea, hypotension, non-cardiogenic pulmonary edema, and fever, which has large potential overlap with ARDs, which is defined clinically as dyspnea, bilateral infiltrates, hypoxemia, and non-cardiogenic edema. Importantly, the mortality rate from TRALI is likely low, in contrast with ARDs. The predominant hypothesis is that donor anti-leukocyte antibodies react with white blood cells within the recipient[25]. A recent analysis of healthy volunteers receiving autologous RBC transfusions demonstrates consistent impaired gas exchange after transfusion[26]. This suggests that RBC transfusions have important immune effects on the respiratory system in the majority of recipients, not just those with obvious TRALI events. More discussion regarding TRALI can be found in the sections regarding plasma blood products.

The association of decreased long term survival and exposure to red blood cell transfusion after cardiac surgery has been reported by several investigators[27] [28]. The mechanism for this decreased survivorship is not well understood, and is likely not explained by infectious events alone. Transfusion exposure may merely be a marker for conditions that limit survival, such as peri-operative hemorrhage. Alternatively, RBC transfusions may exert a long-lasting alteration of a recipient's immune function, thereby impacting long-term survival. The Northern New England Cardiovascular Disease Study Group recently compared long-term survival for patients who were exposed to smaller quantities of RBC transfusions (1 or 2 units) to those who were never exposed to RBC transfusion during their index CABG admission. As a result, this analysis includes patients who were more likely transfused as treatment for stable peri-operative anemia, thereby reducing the potentially confounding factor of substantial blood loss or other hemorrhagic complications. Exposure to small doses of RBC transfusions (1 or 2 units) during admission for cardiac surgery was associated with a 16 percent increased adjusted risk of 5 year mortality in this regional cohort of cardiac surgical patients. The impact on survival was most pronounced in the first 6 months following surgery, with an adjusted hazard ratio of 44 percent (Figure 4). This adverse impact on survival after exposure to RBC transfusion was not explained by differences among patients who received blood nor by procedural characteristics. This was confirmed using propensity score analysis.

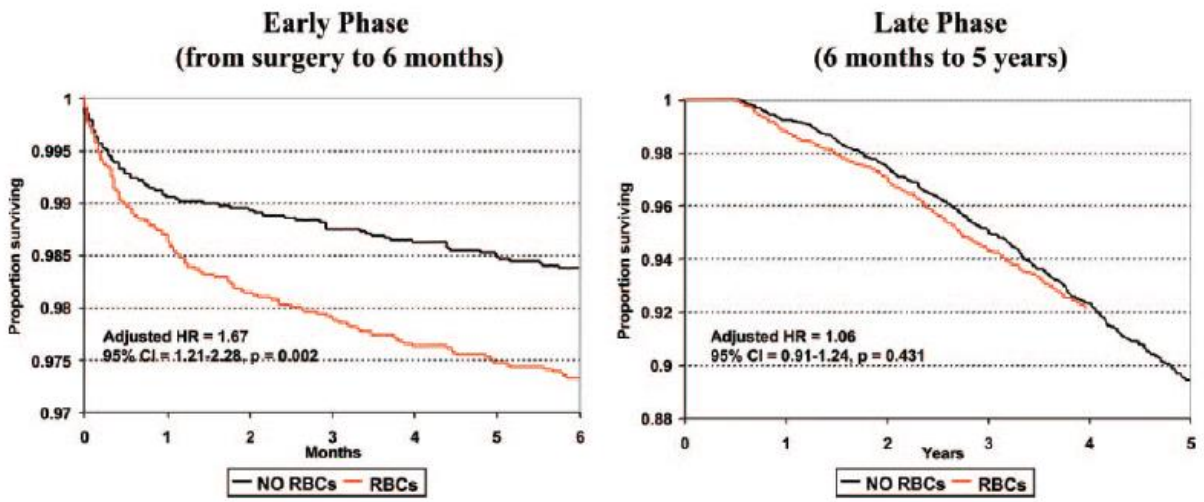

Figure 4. Adjusted Survival by Red Blood Cell Exposure among 9,079 Cardiac Surgical Patients.

Leukoreduction

Because of the concern that donor white blood cells are problematic when administered to the donor during RBC transfusion, strategies to reduce the presence of these unwanted white blood cells have been considered. Leukoreduction has been hypothesized to be capable of reducing the previously described morbidity and mortality related to RBC transfusion. However, meta-analyses of randomized controlled trials on this topic fail to justify universal application of this therapy beyond previously accepted situations[25]. It is important to note that this meta-analysis supported a benefit of leukoreduction in the cardiac surgical population, based on 4 randomized controlled trials. While some have questioned whether the available data at this point supports the considerable expense associated with the universal adoption of this change in transfusion practice, leukoreduction has recently been adapted in Europe and Canada, and is being increasingly adopted in the US[29 30].

Storage of RBCs

A final consideration with RBC transfusions is the "Storage Lesion". This concept considers the predictable changes to red blood cells during storage[31]. There are emerging data that question the efficacy of stored RBCs because of these changes. The goal of administering a RBC transfusion is to increase the hemoglobin concentration and therefore improve oxygen delivery to the tissues. Normal RBCs have a biconcave shape and are quite capable of deforming as they pass through capillaries. During storage, RBCs lose their biconcave shape and become irregular in shape. As a result of these morphologic changes, stored RBCs are less deformable, and more adherent to endothelium[32]. Stored RBCs also become depleted of ATP and 2,3-DPG and these changes may contribute to decreased function. The clinical significance of the storage lesion is not certain.

Platelet Transfusions

A recent review of evidence based indications for platelet and plasma has been completed for the critically ill patient[33]. Stored units of platelets are can be collected by two methods. Regardless of collection technique, units of platelets must be stored at room temperature, kept in constant motion, which results in a short shelf life. They are stored in a special permeable plastic, as they continue to respire during storage. If respiration were not to occur, the platelets would become anaerobic, produce lactate which may not be able to be buffered by the small quantity of plasma in the stored unit, become acidotic and ultimately die.

Transmission of bacterial infection is a significant risk of platelet therapy, and is several orders of magnitude more frequent than transmission of viral infections, as mentioned previously[34]. In addition, the fatality rate due to bacterial contamination of platelets is several orders of magnitude greater than the transmission rate of viral infections, such as HIV or hepatitis C. For the peri-operative or critically ill patient, transmission of bacterial infections via platelet administration is a serious concern.

Potential sources of bacterial contamination of platelet units include the skin of the donor at the time of collection. Less likely sources are bacteremia of the donor, contamination of the collection bag, or contamination

during processing of the unit. The risk of bacterial transmission is greater with platelet units compared to other blood products which are stored at cold temperatures. Currently the risk of bacterial contamination is estimated at 1:2000 to 1:3000. Blood banks currently culture stored platelet units to detect units that are contaminated with bacteria. While this is helpful for reducing the risk of bacterial infection, there are ongoing concerns about both false positive and false negative results. A recent observational study from the American Red Cross reported a confirmed positive contamination rate of 1:5,399, from a pool of all positive cultures (crude rate of all positive cultures was 1:1,641)[35]. In other words, only 30% of all positive cultures from these aphereis platelet units were ultimately confirmed positive. This illustrates the limitation of this screening methodology.

Other risks related to platelet transfusions include TRALI, febrile reactions, and transfusion associated circulatory overload. There are also observational data from CABG surgery patients that describe an association of platelet transfusion with increased risk of stroke, inotrope use, pulmonary dysfunction, as well as death. These associations were significant after adjustment for patient and disease characteristics[36].

Interpreting these risks of platelet transfusions is challenging, because the data to support a benefit for platelet transfusion is lacking. What limited data there is derives from the management of non critically ill hematology and oncology patients who develop thrombocytopenia as a result of chemotherapy. A recent review regarding platelet therapy summarizes the available literature[37]. This review suggests generalizing those guidelines developed for the oncology patients does not make sense. Therefore the decision to use prophylactic transfusions (i.e, keep the platelet count above a certain threshold) or therapeutic transfusions (i.e., transfuse only for active bleeding or immediately prior to a procedure) in the operating room or intensive care unit is not currently clear. In addition what dose of platelets is necessary is not well characterized either.

Fresh Frozen Plasma & Cryoprecipitate

Fresh frozen plasma (FFP) is often administered to patients with elevated prothrombin time (PT) or activated partial thromboplastin time (PTT). FFP does contain fibrinogen, so this product can also be administered to patients with a low fibrinogen. Cryoprecipitate is made from FFP, and contains higher concentrations of fibrinogen, von Willebrand factor, and factor VIII. As such cryoprecipitate is indicated to replete deficiency of these factors. These indications based on abnormal laboratory coagulation studies are most appropriate prior to an invasive procedure that is associated with bleeding risks or during an episode of active hemorrhage. These indications are most often viewed as inappropriate when used to prevent spontaneous bleeding. Also use of FFP as a volume expander is viewed as inappropriate. Unfortunately, none of these indications are evidence-based. Furthermore, there is incomplete evidence that first, the correction of abnormal coagulation studies with FFP is transient in nature (i.e., lasts only 2 to 4 hours), and second that abnormal coagulation studies do not necessarily predict bleeding risk during procedures[32].

While the indications for and benefits of these plasma blood products remain uncertain, some risks related to their use are more clearly understood. Like all the blood products discussed in this review, use of plasma carries risks of infection, allergic reactions, hemolysis, and circulatory volume overload. Data from the United Kingdom (Serious Hazards of Transfusion) Hemovigilance Systems (SHOT) document that allergic reactions are more common with plasma units compared to RBC units[38]. Hemolysis from ABO incompatibility is also possible, because plasma may contain anti-A and anti-B antibiodies that react within the recipient. The “universal donor” is AB type plasma. Recent data from the French and the United Kingdom (Serious Hazards of Transfusion) Hemovigilance Systems document that the risk of transfusion related acute lung injury (TRALI) is also much higher with “plasma-rich” blood components, such as fresh frozen plasma and platelets, compared to RBC transfusions[36]. SHOT data suggests a risk of 1 in 60,000 per unit for plasma transfusion. Interestingly, these data found a strong association of TRALI and female gender of the donor. It is hypothesized that pregnancy may induce human leukocyte or human neutrophil antibodies among these female donors. This has led to the preferential use of male derived plasma for fresh frozen plasma products in some countries.

Massive Transfusion

Observational evidence from Operation Iraqi Freedom and Trauma Centers is informing changes to Massive Transfusion Protocols at many trauma centers[39]. One major change has been the suggested ratio of red blood cell to fresh frozen plasma (FFP) transfusions during resuscitation of the most severely injured and

uncontrollably hemorrhaging trauma patients. An association between red cell to FFP ratios and mortality has led to the recommendation of administering a ratio o f 1:1 or 1:2 for these patients[40]. A randomized trial of these ratios is clearly needed to further investigate whether these observations are indeed valid. Other important considerations during management of these patients include vigilance for and management of hypothermia, acidosis, and hypotension.

General Considerations

Currently, there are three predominate risks to consider when deciding to use blood products: 1. transfusion related acute lung injury (TRALI); 2, bacterial contamination of platelets; and 3. ABO incompatibility. TRALI and bacterial contamination of platelets have been described above. Administration of an incompatible unit of blood is not a new problem, but remains a significant risk today. For example, errors with blood specimens and samples labeled with the wrong patient information are not rare[41]. ABO incompatibility is most frequently related to transfusion of RBCs, but can also occur with platelets and plasma products. Sixty percent of the transfusion related deaths reported to the FDA during 1990-1998 were hemolytic reactions. Every year one to two dozen patients will die simply from getting the wrong blood in the United States. Of note, transfusion of ABO incompatible blood products has recently been introduced as a one of the mistakes that will prohibit payment for hospital care of patients in some states.

Today we are better positioned to optimize our use of transfusions than we have been in the past. This is possible because of a rapid growth in our understanding of not only the risks of anemia, but the risks and benefits of RBC unit storage and transfusion over the last decade. By understanding the current evidence regarding the treatment of anemia with RBC transfusion, we can significantly decrease the local, regional, and national variation currently witnessed for transfusions. Specific to the use of fresh frozen plasma (FFP) and platelets, the risks and benefits of transfusion are less certain. However, there is growing evidence regarding the risks of transfusing FFP and platelets that are relevant when making decisions to administer these products.

In conclusion despite significant advances in the safety of blood therapy, there remain significant risks related to their use. Variation in the utilization of blood products that are not explained by differences in patient and disease characteristics suggest that provider behavior is driving at least some of our national use of blood products. Given the risks to patients that still exist when they are transfused, careful and judicious use of blood products is appropriate.

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Management of the Patient With Pulmonary Hypertension and Right Ventricular Failure

Jacob Raphael, MD — **Charlottesville, VA**
Ronald Pearl, MD — **Palo Alto, CA**

Introduction

Pulmonary hypertension (PH) is associated with significant morbidity and mortality. While disease-modifying therapies in the treatment of PH have dramatically increased the life expectancy of these patients, they still remain at high risk for perioperative complications after either cardiac or non-cardiac procedures [1-4]. Furthermore, PH may lead to right ventricular (RV) failure, which is a predictor of poor outcome. Managing the patient with PH and RV failure requires understanding of pulmonary physiology and how to avoid increases in pulmonary vascular resistance (PVR). Therapies primarily focus on decreasing PVR and supporting underlying RV failure.

Definition of PH, classification and epidemiology

The pulmonary circulation is normally a low pressure and resistance circuit. The normal systolic, diastolic, and mean pulmonary artery pressures (PAP) are 22 mmHg, 10 mmHg, and 15 mmHg, respectively. The PVR is normally 90 to 120 dynes.sec.cm^{-5}.

PH is defined as a mean PAP of greater than 25 mmHg at rest or a PVR greater than 250 dynes.sec.cm^{-5} [5]. A mean PAP greater than 50 mmHg or a PVR greater than 600 dynes.sec.cm^{-5} is considered severe PH. An updated World Health Organization (WHO) clinical classification of PH has recently been published[6]. This classification has 5 major groups: 1) **pulmonary arterial hypertension** (idiopathic, heritable, drug/toxin induced, associated with other pathologies such as connective tissue disorders or hepatopulmonary syndrome); 2) **pulmonary veno-occlusive disease** (persistent PH of the newborn, PH associated with congenital or acquired left heart disease); 3) **PH due to lung disease and/or hypoxia** (chronic lung disease, sleep-disordered breathing, alveolar hypoventilation); 4) **chronic thromboembolic PH**; 5) **PH with unclear/multifactorial mechanisms** (glycogen storage diseases, occlusive tumors etc.). A distinction between pre-capillary and post-capillary PH is fundamental to understanding the vascular and hemodynamic changes present in patients with PH. The characterization of the different hemodynamic profiles of pre or post-capillary disease is summarized in table 1.

Table 1: hemodynamic characterization of PH:

Definition	Hemodynamics	WHO clinical groups
	mPAP > 25mmHg	All groups
1) Pre-capillary PH	mPAP > 25mmHg PAWP < 15mmHg PVR > 250 dynes.sec.cm^{-5} CO normal/reduced/high	Pulmonary arterial hypertension PH due to lung disease CTEPH PH with unclear and/or multifactorial mechanisms
2) Post-capillary PH	mPAP > 25mmHg PAWP > 15mmHg CO normal/reduced/high	PH due to left heart disease

mPAP - mean pulmonary arterial pressure; PAWP - pulmonary artery wedge pressure; PVR - pulmonary vascular resistance; CTEPH - chronic thromboembolic pulmonary hypertension; CO - cardiac output; High cardiac output can be present in cases of hyperkinetic conditions such as systemic to pulmonary shunts (pulmonary circulation only), anemia, hyperthyroidism, portal hypertension, sepsis etc.

PH most commonly observed in the perioperative period is caused by cardiac (post-capillary) or pulmonary (pre-capillary) disease. Left ventricular systolic dysfunction, diastolic dysfunction and mitral valve disease result in elevations in left atrial pressure (LAP). This increase in LAP passively increases the pulmonary venous pressure, PAP, and PVR. Congenital cardiac diseases that cause left to right shunting result in chronic increased pulmonary blood flow that causes hypertrophy and fibrosis of the smooth muscle surrounding the pulmonary vessels - eventually leading

to fixed vasoconstriction and elevated PVR. Respiratory disorders such as chronic obstructive airway disease lead to PH, at least in part, via hypoxia-induced vasoconstriction. PH may initially consist of vasoconstriction only, which is reversible with vasodilator therapy. However, as the underlying pathology progresses, vasoconstriction may result in smooth muscle hypertrophy and narrowing of the vascular lumen. Reversal of smooth muscle hypertrophy is possible over weeks to months with vasodilator therapy. Further progression of the disease involves fibrosis and more fixed disease. Therapy at this point becomes difficult, and attempts to decrease PVR with vasodilators may only result in a decrease in SVR and low blood pressure. Endothelial dysfunction may also lead to decreased prostacyclin to thromboxane ratio, as well as decreased production of nitric oxide (NO)[7,8]. Prostacyclin is a potent vasodilator that inhibits platelet aggregation and smooth muscle cell proliferation[9]. Thromboxane A_2 stimulates vasoconstriction and platelet aggregation. Nitric oxide (NO) acts via cyclic guanosine mono phosphate (cGMP). NO causes vasodilatation and has antiproliferative properties [8]. All forms of PH are believed to result in a state of reduced NO bioavailability [10]. Phosphodiesterase-5 (PDE-5) breaks down cGMP into inactive 5GMP. In patients with PH there is increased expression of PDE-5 both in the endothelial smooth muscle cells and in the right ventricle [11]. There is also an association between PAH and increased production of endothelin-1 (ET-1) in the pulmonary vasculature. This substance is a potent vasoconstrictor that stimulates smooth muscle cell proliferation [8,11,12]. Therefore, the main focus of treatment of PH is reversal of vasoconstriction using endothelin-1 receptor antagonists (Bosentan, Ambrisentan, Macitentan), prostanoids (Epoprostenol, Iloprost, Treprostinil), PDE-3 or 5 inhibitors (Milrinone or Sildenafil, Tadalafil, respectively) and direct vasodilator therapy, mainly inhaled NO.

Pulmonary vascular resistance (PVR)

In contrast to the systemic circulation, the pulmonary vessels have relatively thin walls and the vascular smooth muscle is sparsely distributed in the smaller arterioles. As such, increases in CO distend open vessels and recruit previously closed vessels resulting in a decrease in PVR. Clinically, this means that increasing CO with inotropic agents or increasing blood volume will passively decrease PVR. This relationship becomes less pronounced in disease states of the pulmonary circulation. The endothelium plays an important role in maintaining low resting pulmonary vascular tone. Endothelial dysfunction and alterations of endogenous vasodilators is associated with the development of PH [13]. An important aspect in treating PH is understanding how certain factors alter PVR. Oxygen has a significant effect on PVR, with alveolar hypoxia being a potent vasoconstrictor. Small areas of alveolar hypoxia cause diversion of blood flow and minimal changes in PVR. In this context, hypoxic pulmonary vasoconstriction (HPV) is a protective mechanism that improves ventilation/perfusion matching. This becomes important when treating PH because all intravenous vasodilators inhibit HPV and may decrease PaO_2. Larger areas of hypoxia produce proportionally greater increases in PVR and thus increase in PAP. Acidosis is another potent vasoconstrictor, whereas alkalosis vasodilates the pulmonary circulation. Hypercapnia and hypocapnia most likely alter PVR via their effects on pH. Atelectasis can increase PVR via stimulation of HPV and mechanical compression; therefore, the lungs should be adequately expanded in patients with PH, yet it is important to remember that PEEP can result in over-inflation, which by itself can result in increase in PAP. Providing adequate oxygenation and treating acidosis (respiratory or metabolic) represents one of the most important and first line treatments of PH. Sympathetic stimulation, hypothermia, and catecholamines are also important factors that increase PVR.

Adrenoreceptors: α-1 and β-2 adrenoreceptors are the most clinically relevant receptors in the pulmonary vasculature. β-2 agonists decrease PVR, whereas α-1 agonists increase PVR. These receptors are less densely distributed on pulmonary vessels compared to the systemic circulation, hence one would expect the effects of agonists to be decreased. Furthermore, the tone of the pulmonary circulation is normally low, therefore β -2 stimulation normally has little effect; however, in the presence of PH β-2 agonists decrease PVR. α-1 agonists increase PVR but not to same extent as the systemic vascular resistance (SVR)[14] because the pulmonary circulation contains relatively less vascular smooth muscle. β-2 receptors responsible for vasodilation are on the endothelium; therefore, their effect may be decreased in the presence of endothelial dysfunction.

The Right Ventricle (RV)

The right ventricle is a thin walled, crescent shaped structure that is suited for volume work, in contrast to the thick walled LV that is suited for pressure work. While the LV maintains a constant output over a wide range of afterloads, RV function is more sensitive to changes in PAP. An acute increase in mean PAP above 40 mmHg results in a decrease in RV ejection fraction, even in the presence of normal RV contractility. In the presence of decreased RV contractility

the RV is even more sensitive to acute increases in afterload. On the other hand, more gradual changes in PAP may allow time for the RV to hypertrophy and sustain a relatively normal output. Coronary blood flow to the RV normally occurs throughout both systole and diastole because of the continuous pressure gradient (coronary perfusion pressure, CPP) between the aorta and the RV. The RV blood/oxygen supply is proportional to the systemic pressure and inversely proportional to the RV pressure. Systemic hypotension or increased RV pressure may result in decreased RV CPP. RV oxygen demand is proportional to the RV pressure, RV volume and heart rate. Hence, increased RV pressure not only decreases RV oxygen supply but also increases oxygen demand. Therefore, decreasing PAP with the use of vasodilators to facilitate decrease in RV pressure is critically important in treating PH and RV failure. Yet, at the same time it is important to avoid decreasing systemic pressure, which could result in a drop in CPP.

Right Ventricular Failure

RV failure is most commonly caused by acute or chronic pressure overload. While acute increases in RV afterload are poorly tolerated, more gradual increases in pressure overload of the RV is sometimes tolerated for years before symptoms and signs of RV failure become evident. In the presence of a chronic buildup of PH the RV may hypertrophy and be able to generate systemic pressures. Nevertheless, PH eventually leads to RV dilation, decreased RV stroke volume, and decreased global cardiac function. Ischemia and infarction may also contribute to RV failure. Although angina generally occurs because of LV ischemia, ischemia may also arise from a decrease in RV coronary blood flow or increased RV oxygen demand. RV ischemia may also result from inadequate myocardial protection during cardiopulmonary bypass (CPB). Volume overload from tricuspid regurgitation (TR) or atrial septal defects may also contribute to RV failure.

Common symptoms of PH and RV failure are dyspnea, fatigue, reduced exercise tolerance, syncope and chest pain. Signs of PH and RV failure include peripheral edema, tachypnea, tachycardia, distension of the neck veins and hepatomegaly. RV lifts may be palpated and tricuspid regurgitation auscultated. The CVP, which is normally less than 5 mmHg, may increase to above 20 mmHg in the presence of RV failure. PH and RV failure can also alter LV function. Interdependence between the ventricles occurs in the presence of increased PVR and RV end-diastolic volume and pressure, such that the intraventricular septum shifts towards the LV cavity[15]. PH increases RV afterload, which may increase RV pressure and volume, while decreasing RV stroke volume. This may cause a decrease in LV preload and thus a decrease in systemic cardiac output (CO). Increased RV volume and pressure may also decrease coronary blood flow and worsen RV ischemia, which will further deteriorate CO. Treatment of PH may include vasodilators to decrease PVR, inotropic agents to improve RV function, optimizing ventricular volume, and correction of acid base and oxygenation status. In order to treat PH and RV failure continuous assessment of hemodynamics may be required. Patients may be best monitored with an arterial line and PA catheter. Transesophageal echocardiography (TEE) is an important tool that can guide the clinician in diagnosis and patient management. It is important of understand whether the patient has RV failure, PH, or both. Treatment of patients with PH without RV failure consists primarily of the use of vasodilators. In contrast, patients with RV failure without PH may be treated primarily with inotropic agents and possibly diuretics or vasoconstrictors. Patients with PH and RV failure usually require careful tailoring of both vasodilators and inotropic agents.

Diagnosis and treatment

Echocardiography remains the method of choice for screening and assessing the likelihood of PH and for evaluation of RV function. Right heart catheterization is the gold standard to confirm the diagnosis and establish the severity of PH. Assessment of the RV by echocardiography is not as straightforward as evaluation of the LV; however RV function can still be evaluated. Signs of RV dysfunction include hypokinesis of the RV free wall, RV dilation or hypertrophy, a change in the normal crescent RV shape to round, and flattening or bulging of the interventricular septum from right to left. RV hypertrophy is characterized by RV free wall thickness greater than 5 mm at end-diastole. RV dilation is also defined by an end-diastolic cross-sectional area of greater than 60% of the LV. Right ventricular systolic impairment also decreases tricuspid annular plane systolic excursion (TAPSE). In addition, tricuspid regurgitation is common in patients with PH and RV failure and the velocity of the TR jet is used to estimate the PAP (using the Bernoulli equation).

The treatment of patients with PH is divided into general supportive measures and specific drug therapy. General measures include treating underlying conditions that may cause PH, as well as advice on physical activity and supervised rehabilitation, infection control, birth control and pregnancy management. Supportive measures include advice on anticoagulation, diuretics and oxygen therapy.

Drug therapy includes calcium channel blockers that have traditionally been used in the treatment of idiopathic PH although this therapy is effective in only a small fraction of the patients[16]. Synthetic prostacyclin analogues, such as epoprostenol, iloprost and treprostinil, have shown efficacy in patients with idiopathic PH. Epoprostenol has a short half-life and is stable at room temperature for only 8 h, hence, it needs to be administered via continuous intravenous infusion or by inhalation. Iloprost is available for intravenous, oral, and aerosol administration. Inhaled iloprost in patients with idiopathic PH and CTEPH showed an improvement in symptoms and clinical events[17,18]. Another group of drugs - endothelin receptor antagonists (Bosentan, Ambrisentan and Macitentan) are effective in the treatment of PH. Studies have demonstrated improved exercise capacity[19], hemodynamics and time to exacerbations[20], as well as, decreased mortality[21]. Phosphodiesterase-5 inhibitors, such as sildenafil and tadalafil, are orally active, potent pulmonary vasodilators. The use of these drugs results in improved exercise capacity, symptoms and hemodynamics in PH patients[22,23]. Riociguat is a novel medication that stimulates soluble guanylate cyclase, leading to an increase in cyclic GMP, and has proven to be effective in idiopathic PH and CTEPH patients[24]. In selective patients heart–lung transplantation or double-lung transplantation may be indicated[25].

Anesthetic Management

Preoperative evaluation

Patients need to be explicitly informed of the possibility of serious complications that can lead to prolonged hospitalization or even death. The mortality associated with surgery is influenced by the severity of PH and type of surgery. Most studies that investigated perioperative outcomes in patients with PH are small retrospective case series[2,26,27]. A much larger investigation by Memtsoudis et al. matched 3302 PH patients who underwent total hip or knee arthroplasty with non-PH controls. The PH group showed a 4 to 4.5-fold increase in the adjusted risk of mortality after hip or knee arthroplasty compared with patients without PH. The highest mortality was reported in patients with idiopathic pulmonary arterial hypertension[4].

The pre-operative evaluation of a patient with PH should be based on a risk assessment that takes into account their functional state, severity of the disease and type of surgery. A detailed history and physical examination should be complemented with relevant additional studies. New York heart association (NYHA) functional class at diagnosis is an important predictor of survival and improvement from functional class 3/4 to 1/2 with treatment is associated with a better prognosis. The six-minute walking distance (6MWD) is used to assess exercise capacity in patients with PH and a reduced total distance to less than 300m is associated with higher mortality[28]. Pre-operative tests include laboratory studies, ECG, echocardiography, chest radiography and a recent right heart catheterization. Echocardiography is non invasive and readily available to assess ventricular function and the severity of PH. Echocardiographic predictors of poor outcome include right atrial enlargement, reduced tricuspid annular plane excursion and pericardial effusion[29]. Right heart catheterization confirms the diagnosis of PH, evaluates RV function and provides differentiation between pre-capillary and post-capillary PH. Prior to surgery the patients' medications need to be reviewed and therapies optimized. Anti PH medications should be continued and when oral formulations cannot be taken, temporary administration of inhaled (inhaled NO, Flolan) or intravenous (prostacyclin, milrinone) formulations should be considered.

Monitoring

Invasive arterial blood pressure monitoring before induction can facilitate early recognition of hemodynamic instability and allows intermittent arterial blood gas sampling to evaluate ventilation adequacy of. Intraoperative monitoring with TEE and/or a pulmonary artery catheter should be considered in all patients with severe PH or mild-to-moderate PH with existing right-sided heart failure[30]. Use of TEE allows assessment of systolic pulmonary artery pressure, provides information on right ventricular performance and helps guiding fluid management. Studies have shown that the use of TEE triggered a change in the overall therapeutic management in as much as 50% of high-risk patients undergoing non-cardiac surgery[31,32]. The intra-operative use of a pulmonary artery catheter (PAC) is controversial. Most studies failed to demonstrate any benefit in its use for intra-operative monitoring[33]. Nevertheless, its use in the perioperative setting provides direct continuous measurement of pulmonary artery pressure, pulmonary vascular resistance and dynamic changes that occur in response to fluid administration or drug therapy. Furthermore, although there was no reduction in mortality[34], the use of a PAC can provide crucial continues measurements postoperatively in the intensive care unit. It is important to remember though, that PAC placement is associated with certain risks, which must be considered before insertion is attempted.

Anesthetic induction and maintenance

Anesthetic induction in patients with PH and RV failure may be challenging. Prevention of PH crisis and RV failure relies on the optimal mechanical matching of the right ventricle and pulmonary circulation. These patients often have high baseline sympathetic tone and may be catecholamine deprived. As such, these patients may be prone to severe hemodynamic compromise upon anesthetic induction[35]. Titrated doses of narcotics, etomidate, or ketamine may be appropriate, with maintenance of systemic pressure the primary goal. Nitrous oxide and ketamine increase PVR in patients with PH, although neither increases PVR in pediatric patients. Volatile anesthetics are unlikely to have significant effects on PVR, but they depress myocardial contractility and should be used very cautiously in patients with severe RV failure. Table 2 summarizes the effects of various anesthetics on RV contractility and afterload. In patients undergoing peripheral procedures, regional or peripheral blocks may be ideal if preload and afterload can be maintained.

Table 2: Effect of anaesthetic agents on right ventricular (RV) contractility and pulmonary vascular resistance[36-41]

Anesthetic Agent	Isoflurane/ Desflurane	Sevoflurane	N_2O	Etomidate	Ketamine	Propofol	Opioids
RV contractility	↓↓	↓↓	↓	↔	↓	↓↓	↔
PVR	↑	↔	↑↑	↔	↑ adult ↔child	↓	↔

↓↓-marked decrease; ↑↑-marked increase; ↑-increase; ↓-decrease; ↔ no change

The transition from spontaneous breathing to positive pressure ventilation may significantly increase PVR and RV afterload. While this has minimal effect in patients with normal RV function, in patients with PH and RV failure lung hyperinflation or excessive positive end-expiratory pressure (PEEP) can drastically decrease CO. Thus, optimal ventilation strategies may include a low tidal volume and low PEEP, while avoiding hypercapnia. Other factors such as patient positioning, pneumoperitoneum or diaphragmatic compression can also increase right ventricular afterload and precipitate a pulmonary hypertensive crisis. Every effort should be made to avoid hypoxia, hypercarbia and acidosis since they may significantly increase PVR. An adequate depth of anesthesia should be ensured before attempting laryngoscopy and tracheal intubation, as sympathetic stimulation has deleterious effects on right ventricular afterload.

In general, patients with PH have low systemic arterial pressures, rendering them susceptible to decompensation. The goal is to maintain the pre-anesthetic hemodynamic condition. Therefore, invasive monitoring before induction is often required. The use of a low dose of vasoconstrictor, such as norepinephrine or vasopressin, to compensate for the reduction in systemic vascular resistance caused by anesthetic drugs is a safe and effective approach. Volume loading will increase RV output in the absence of PH if RV contractility is normal. However, if decreased contractility and PH accompany RV failure then volume loading may be detrimental. In this situation, volume loading may cause RV dilation and result in a decrease in LV volume and CO. The most appropriate action is to assess the effects of volume loading by measuring the CO and following RV and LV function by TEE. In the presence of RV volume overload, venous vasodilation with nitroglycerin or diuretic therapy may improve RV function.

Maintaining the gradient between aorta and right ventricle is achieved by using sympathomimetic and non-sympathomimetic vasopressors. Norepinephrine and vasopressin improve perfusion of the right coronary artery, reduce the pulmonary/systemic vascular resistance ratio, enhance right ventricular performance and marginally improve cardiac output[42,43]. However, there is marginal evidence regarding their impact on mortality related to right heart failure[44]. Inotropes that enhance right ventricular performance, such as epinephrine, dobutamine and levosimendan are effective in treating right-sided heart failure. The use of inotropes has a modest impact in reducing the overall mortality related to PH, and their wide availability and ease of administration make this group of drugs very attractive for use in the perioperative setting. Inodilators, such as the phosphodiesterase-3 inhibitors (milrinone) have been shown to be beneficial when compared with conventional inotropic support only [44]. It appears that the influence of phosphodiesterase-3 inhibitors on reducing pulmonary vascular resistance is more pronounced than the reduction in systemic vascular resistance. Nonetheless, reduction in systemic vascular resistance can compromise right coronary artery blood flow in patients with severe PH and therefore they should be administered cautiously.

In 2010, the phsphodiesterase-5 inhibitor, sildenafil, was approved for intravenous therapy of PH and it may be an attractive option for the perioperative management of patients that are already on this medication.
Selective inhaled pulmonary vasodilators (inhaled NO or prostacyclin) have essentially no effect on the systemic blood pressure. These drugs improve oxygenation by decreasing pulmonary shunt, which is important in patients ARDS-associated PH. Inhaled NO acts by diffusing from the alveoli into the pulmonary vascular smooth muscle to stimulate the production of cGMP which results in vasodilation. NO is prevented from producing downstream systemic vasodilation because it rapidly binds to hemoglobin and becomes inactive. Inhaled PGI2 increases smooth muscle cAMP to cause pulmonary arterial vasodilation but is hydrolyzed before producing systemic effects. Inhaled vasodilators also have the potential to increase PaO_2 in patients with ventilation/perfusion abnormalities. Since these drugs are inhaled, vasodilation is primarily limited to areas that are ventilated, and hence, ventilation/perfusion matching is improved and shunt is decreased. It has been reported that the use of inhaled NO over a prolonged period is associated with rebound phenomena and direct toxicity to the lungs[45]. Prostacyclin and its analogues offer a good alternative to NO and there are several reports of the use of inhaled prostanoids in the perioperative setting[46-48]. Both NO and prostacyclin can increase bleeding because of platelet inhibition, although this is usually not clinically significant. While inhaled NO is delivered as a gas via a specialized delivery system, PGI2 and the other agents are delivered as simple nebulized drugs.

Postoperative management
Most patients with PH should be recovered postoperatively in the intensive care unit. There should be a robust plan for pain management, including regional blocks and non-opioid medications. Respiratory failure (60%) and right ventricular failure (50%) are the most frequent contributing causes to morbidity or mortality[1]. Atrial tachyarrhythmias are associated with right ventricular failure and death. Beta-blockers should be avoided as they are poorly tolerated in these patients[49], hence amiodarone would be the drug of choice. Post-surgical complications such as bleeding and infection must be promptly controlled and treated. Right ventricular function in PH is 'preload-dependent' but at the same time, fluid overloading is detrimental. Maintenance of systemic pressures with vasopressors and inotropes, along with replacement of blood volume when necessary, is of paramount importance. Vasodilator therapies that were started intraoperatively must be continued and slowly transitioned back to the patient's pre-operative regimen.

PH and pregnancy
Historically, it is well known that pregnancy poses a very high risk to women with PH. Avoidance of pregnancy is still strongly advocated and early termination is recommended for PH patients. Endothelin receptor antagonists are contraindicated during pregnancy due to their teratogenic effect, but prostacyclins, PDE inhibitors and inhaled nitric oxide can be used[50]. Calcium channel blockers may also be indicated.
While earlier studies reported a mortality rate as high as 50% in pregnant women with PH[51], more recent data shows a lower mortality rate, yet still not insignificant[52,53]. While vaginal delivery is associated with reduced risk for maternal bleeding and infection, Elective caesarean section allows for better planning, a multidisciplinary team approach and optimal pain control. While in most centers elective caesarean section will be the method of choice for delivery, the optimal anesthetic technique (GA vs. neuraxial blockade) is still under debate[54,55]. The majority of deaths in pregnant patients with PH occur in the postpartum[53] period, mainly due to right heart failure and pulmonary thromboembolism, thus thromboprophylaxis in pregnant patients with PH while not universally indicated is of prime importance[50].

Conclusions
Recent advances in the management of patients with PH and RV failure and new treatments have improved patient outcomes, nonetheless these are extremely high-risk patients that require a multidisciplinary team approach in specialized centers. There is an increasing number of patients presenting for either cardiac or non-cardiac surgery. Their successful management requires a thorough pre-operative risk assessment. Correct diagnosis, optimization of the patient's functional status and hemodynamics and management of co-morbidities are vital. Anesthetic management is dependent on an understanding of pathophysiology and avoidance of a pulmonary hypertensive crisis. Postoperative care should be in the setup of an intensive care unit with the understanding that the majority of complications occur in the postoperative period.

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Working Hard – Hardly Working: Measuring Clinical Productivity of Individual Anesthesiologists

Amr Abouleish, MD, MBA **Galveston, Texas**

Preface

At the 2001 ASA Annual Meeting, I was fortunate to give a refresher course lecture on this topic for the first time. At that time, anesthesiology groups were focused on primarily providing surgical anesthesia care. Hospitals and payers were only valuing this type of clinical care from anesthesiologists. Since then, there has been a shift, that is accelerating the past several years, from only valuing surgical anesthesia care to also including other activities (both clinical and organizational) and quality care. Today, it is essential for anesthesiologists and their groups to do more than simply "pass gas". Therefore, in this refresher course lecture I still cover issues of measuring surgical anesthesia care, but I have added the second half focusing on possible incentives (that is behavior modification system) for other activities that groups need to promote or value to be successful now and in the future.

Introduction

In science, the "observe effect" refers to changes caused by the act of observation or measurement. In behavior theory, this effect is also known as the Hawthorne effect and defined as the process where human subjects of an experiment change their behavior simply because they are be being studied. A similar process often occurs when one measures an individual's activities (or behavior). One of the goals of measuring behavior, in this case clinical productivity, is to increase productivity and reward those that do more work. In other words, the measurement system can be viewed as behavior modification system.

In any behavior modification system, among the important components is to identify the behavior one wants to promote, to determine how to measure it, and then communicate the process to the individual. In other words, the measurement should value the behavior the group feels is important to the group's success and devalue the activities that are not important or undermines the group's success.

In this presentation, I will first examine the traditional clinical productivity measurements – focused on surgical anesthesia. Then I will discuss behavior modification systems and how they could be applied to not only surgical anesthesia care but to other activities that groups now must perform in order to be successful.

Measuring Surgical Anesthesia Productivity of Individual Anesthesiologists

Two important concepts that one should understand before looking at measuring clinical productivity are (1) individual measurements are not necessarily the same as group measurements, and (2) the difference between internal comparisons and external (benchmarking) comparisons.

Individual and group measurements are not the same thing. The difference is an important concept to understand. Unfortunately, it is not uncommon for comparisons of groups to apply group measurements as benchmarks for work done by an individual. Further, the measurements used to compare groups may not be applicable to comparing individuals as illustrated in this following example using team sports. In basketball, individual measurements include many different statistics for each position, such as assists for point guards, rebounds for power forwards, and blocked shots for centers. In contrast, the meaningful external team comparison (i.e., team comparison) is simply the win-loss record. Anesthesiologists understand this concept well. Within a group, every anesthesiologist does not need to be expert in every subspecialty, as well as quality reporting, contract review, or leadership activities. The best group is a group where leaders have matched demand with the correct individual. That is the pediatric anesthesiologist is providing pediatric anesthesia while the cardiac anesthesiologist is assigned adult patients with cardiac comorbidities or having cardiac surgery – not the other way around. Similarly, with the concept of Perioperative Surgical Home (PSH), not every anesthesiologist needs to do every component of PSH, but the group needs to have anesthesiologist who are experts (or champions) of different aspects.

Further, when comparing individual work, a group wants to compare individuals WITHIN the group and not with anesthesiologists outside the group (i.e., internal comparisons). That is for a private-practice group, measurements of

individual work are used to determine how much of the revenue each individual WITHIN the group will receive. *Because of this essential characteristic, the group can choose their own unique internal measurements and comparisons that will allow the group to best succeed.* In contrast, comparisons of group productivity can be done WITHIN a group over time (i.e., internal comparisons) or can be done with OTHER groups (i.e., external comparisons). The internal comparisons of group work can be similarly defined as the group wishes. In contrast, external comparisons need to be standardized among all the groups and allows for benchmarking. (Note. I will not be covering group productivity measurements in this presentation.)

Why is Measuring Surgical Anesthesia Productivity Not Simple?

Although educational, research, and administrative productivity may be measured similarly in anesthesiology and in non-anesthesiology specialties, measuring clinical (surgical anesthesia) productivity in the discipline of anesthesiology, either for individuals or departments, poses unique challenges because of the need to staff operating rooms (ORs), which is independent of workload, the different billing system, the need to use the right "full-time equivalent (FTE)," and confounding factors.

STAFFING NEEDS AND WORKLOAD

One of the goals for measuring clinical productivity is to determine the proper staffing needed to perform a set amount of work. Unfortunately, for the specialty of anesthesiology, this approach is not logical because workload or productivity measurements cannot be used directly to determine the number of anesthesiologists needed. To illustrate this disconnect between staffing needs and workload, the reader should answer the following question for his/her group: For the next month, what determines the number of anesthesiologists the group needs to staff its anesthetizing sites? The primary determinants of staffing needs are the number of clinical sites to be staffed and the staffing ratio (i.e., concurrency). Other determinants include whether or not a second shift is needed in the evening and the number of staff who are on-call or post-call.(4) Workload and productivity measurements do not determine the number of staff a group needs. In other words, if an anesthesiology group needs to provide care for 20 ORs at 7:30 AM, the number of anesthesiologists required is no different if all the ORs finish at noon or 3 PM! Instead of determining staffing needs, workload or productivity measurements should be used to determine the appropriate number of ORs needed—assuming this decision is based solely on these two variables.

CONFOUNDING FACTORS – ANESTHESIA-INDEPENDENT FACTORS

Confounding factors affect productivity measurements and make comparisons of the measurements less accurate. In measuring the productivity of anesthesia care providers, many times these confounding factors are independent of the anesthesiologist's discretion and hence are also known as "anesthesia-independent" factors. To illustrate the confounding factors of surgical duration, type of surgery, schedule "not full," and obstetric anesthesia care, a hypothetical OR suite will be used as an example. In this OR suite, the anesthesiology group must staff four ORs as well as a labor and delivery suite. For the example, work performed from 7:30 AM to 4:30 PM and the resultant billed ASA units will be examined.

If one assumes that any anesthesiologist can staff any of the rooms, then differences in billed units (base, time, and total units) are related to non-anesthesiologists. Between OR 1 and OR 2, speed of surgery accounts for the differences. Between ORs 1 and 3, type of surgery is the factor. OR 4 represents situation where the surgeon cannot be in the OR after 12 noon. Hence, the OR is open but unused. The difference in billed units between OR 4 and OR 2 has to do with the schedule not being full. Finally, obstetric anesthesia is not billed the same as OR care. In this example, only "face-to-face" time is billable and hence only 1 hour of a 6-hour epidural is billed. (Table 1)

Measuring Surgical Anesthesia (Clinical) Productivity of Individual Anesthesiologists

Because only internal measurements are used for individual measurements, each anesthesiology group can develop and choose productivity measurements of individual anesthesiologists that work best for helping the group be successful. The real question facing the group concerns which measurement is the best indicator of productivity. The answer to this question is different for every group. The right measurement is the measurement that will value services that will help the group succeed and meet its clinical obligations. It is essential that the group's leadership understand what each productivity measurement values and devalues before determining which measurement is right for the group.(8)

Individual Productivity Measurements for Surgical Anesthesia

For the specialty of anesthesiology, individual productivity measurements for Surgical Anesthesia can be categorized into three general groups: total charges (or total ASA units [tASA]), time, or shift-worked. Examples of total charges or tASA billed are the compensation distribution plans of many private-practice groups. If a partner is responsible for 20% of the charges or tASA billed, then that partner receives 20% of the revenue. Because anesthesia care is billed using time units, time-based measurements offer an attractive method for tracking work done by each anesthesiologist. Two different methods, time units billed (TU) and billable time units, have been described previously. Under either of these systems, if a partner bills 20% of the time units, then the partner would receive 20% of the revenue. In the last category, anesthesiologists are credited with working shifts. Some anesthesiology groups use a complex point system with different values for different calls (or late shifts) and different day schedules. However, a more simple system has been described. A "shift-worked" measurement addresses the major daily clinical challenge for any anesthesiology group—having enough anesthesiologists available to be able to provide care at all the anesthetizing sites.

Utilizing Table 1's hypothetical OR suite, we will assume that the anesthesiology group is a physician-only group, and that each physician covers only one anesthetizing site. Therefore, the billed units per OR equals the billed units per FTE. (The issue of concurrency will be discussed later.) For a detailed evaluation of each of these measurements, the reader is referred to reference 1.

Total Charges or tASA Billed Measurements. For this category, the measurement tASA/FTE will be used to demonstrate what is valued and devalued by this group of measurements. Assuming the anesthesiologist group is a physician-only practice, each FTE or anesthesiologist will care for only one room. Therefore, tASA/FTE equals tASA billed for the ORs. The highest tASA/FTE is OR 3—this illustrates that specialty care with high base units is valued by this measurement. The second highest value is OR 1, which has the fast surgeon. The faster the surgeon, the more cases can be done, and hence, the more base units can be billed for the same amount of time. The lowest values are found in OR 4, where downtime is not billed, and in labor and delivery. Both are undervalued with this measurement.1 If all the ORs could be covered by any anesthesiologist in the group, then the differences in tASA/FTE for the one day would be dependent on the "luck of assignment."

Time Measurements. For this category, TU/FTE will be used to demonstrate what is valued and devalued. Again, assuming that we are dealing with a physician-only group, TU/FTE for one day equals the TU billed for the OR. In contrast to tASA/FTE, specialty care (OR 3) no longer has the highest value, and, on the contrary, is devalued because base units are not included in this measurement. In addition, the slowest surgeon (OR 2) now has the highest value, a fact which illustrates that minimum downtime (less turnover time) is valued over the number of cases done. Analogously, downtime in the schedule (OR 4) is undervalued. Finally, obstetric care is very undervalued because of the methodology of billing time units. Again, if any anesthesiologist in the group could cover any of the ORs, then the differences in TU/FTE for one day would be dependent on the "luck of assignment."

Shift-Worked Measurements. In this category, a point system is used to value the shifts worked by an anesthesiologist. The system may be very complex, with different point-values for different shifts as well as other functions (e.g., schedule runner or administrative day for the president of the group). A simple system that values all the shifts the same uses the measurement clinical days worked per FTE (CD/FTE). A CD is defined as working a day providing clinical services independent of billing methods. So unlike tASA/FTE and TU/FTE, this measurement includes anesthesiologists working in a day surgery preoperative clinic (DSU preop), a pain management clinic, an intensive care unit, and a recovery room. If one anesthesiologist were to cover each room, then the CD/FTE would be equal to one for each site. This measurement places the highest value on the anesthesiologist being available at the start of the day to cover clinical sites—the primary day-to-day challenge of any anesthesiology group. Since all services are equal, specialty care (base units) is devalued. On the other hand, because the type of surgery, surgical duration, or downtime do not affect this measurement, "luck of assignment" is not an issue.

Concurrency and Individual Productivity Measurements

Unlike other medical specialties, an anesthesiologist can bill professional services on more than one patient at the same time (i.e., an anesthesiologist can provide concurrent care through the medical direction of an anesthesia care team). The staffing ratio, or concurrency, is defined as anesthetizing sites (OR sites) per anesthesiologist. Differences

in concurrency confound the productivity measurements of individuals and groups. The effect on individual measurements is illustrated below, and the effect on group comparisons will be discussed later.

Using the hypothetical OR suite in Table 1, let us assume that ORs 1, 2, and 4 (all laproscopic cholecystectomy surgery) are cared for by one anesthesiologist ("Dr. A") and three other providers (a certified registered nurse anesthetist [CRNA], an anesthesia assistant [AA], or a resident), while the other anesthetizing sites are personally performed by anesthesiologists ("Dr. B" and "Dr. C"). As a result of different concurrencies, "Dr. A" now has the highest tASA/FTE and TU/FTE because all billed units for OR 1,2, and 4 are credited to "Dr. A," while "Dr. B" and "Dr. C" only have one anesthetizing site credited to each of them. In contrast, CD/FTE is not influenced by concurrency differences and each anesthesiologist has the same value (i.e., one). Therefore, the total charges measurements (tASA/FTE) and the time measurements (TU/FTE) both value a high concurrency or staffing ratio.

Behavior Modification Systems and Incentives for Activities beyond Surgical Anesthesia performed by Individual Anesthesiologists

As noted earlier, an anesthesiology group cannot be successful or even retain hospital contracts if all they do is provide surgical anesthesia. Groups now need to perform activities beyond surgical anesthesia including, but not limited to, to also provide care in preoperative and postoperative periods (e.g., perioperative surgical home components), lead clinical improvement activities (including OR throughput), demonstrate high quality of care, and provide physician leadership to hospital committees and activities. Therefore, group leaders find themselves trying to measure these activities. There is wide spread “frustration” because there is no standard measurements for many of these activities. But this should not be a major issue since the group’s goal is to value these activities and promote individuals to do more of these activities. By definition, the group is seeking to change individual’s behavior and hence looking for “measurements” for behavior modification. Further, behavior modification system are very specific to each group and hence, industry standard measurements are not necessary.

Differences between Variable Pay and Incentive Systems

Incentive pay systems are focused on rewarding or compensating activities that would not necessarily be done (considered a “hardship”) but are essential for the group’s success. In this system, the incentive pay is a smaller part of the overall compensation (e.g., 20%), where the majority of compensation is found in a non-variable base salary. The advantages of the incentive system is that it is simpler to set-up, manage and understand as well as providing more timely feedback. (4)

In contrast, a variable pay system has a very small non-variable base salary and the majority of the compensation is variable. In this system, the variable pay system measures all activities, not only the ones that people don’t want to perform. In other words, much of the pay system will not change behavior but “pays for work done” – even if one would do it if paid a base salary.

The discussion below on behavior modification systems will focus on incentive pay systems only.

Behavior Modification Systems

In the simplest terms, an incentive pay system is an example of a behavior modification system. That is a behavior modification is often viewed as a three-part system (Figure 1): antecedent (manager and employee set a goal), employee behavior (does the employee meet the goal), and consequence/contingent reinforcement (No –consequence, Yes – consequence). But effective behavior modification systems are more complex than a simply setting goals. Further, although financial compensation is often viewed by leaders as how to change behavior but as discussed below, this is not necessarily the best method.

A more complete diagram of Behavior Modification Systems can be seen in Figure 2. The basic three-parts are still seen in the diagram.

Antecedent. “Identifying relevant behavior” is one of the major challenges in a behavior modification system. Group leaders need to ask themselves “What new behaviors/activities do we need individuals to focus on?” Be very careful answering this question. First, the common adage “If it ain’t broke, don’t fix it” should be followed. If there is no

problem with the behavior, don't try to measure it and reward it. Second, beware of the concept of "The folly of rewarding A, hoping for B." (6) Once the relevant behavior is identified, then measuring and charting the behavior needs to be done to validate the measurements to both the leaders and the employees.

Contingent Reinforcement. In the simple model, the manager and employee agree on a goal and then the employee is rewarded when he/she meets the goal. This is the definition of contingent reinforcement – a response is contingent on the behavior – but does not fully describe the possible reinforcements that exist. Reinforcements can be done to maintain or increase the frequency of a *desirable* behavior OR can be done to decrease or eliminate the frequency of an *undesirable* behavior.

Positive Reinforcement. Goal: To increase frequency of *desirable* behavior. This is the most effective and most common reinforcement type. In the work place, money or compensation is often thought to be the most effective, but in reality, money is not always the most effective reward. Non-financial rewards include verbal approval from leader, assignment to desired tasks, titles/promotion, extra time off, and more employee control of activities (ownership of workflow, independence, input on decision making). It is important to note that the highest job satisfaction will occur not when the compensation is highest, but instead when compensation is at market value (median) and the work environment is rewarding.

Negative Reinforcement. Goal: To increase frequency of *desirable* behavior. It is important to differentiate Negative Reinforcement from Punishment (see below). Negative reinforcement is used to increase desirable behavior, while punishment is used to eliminate undesirable behavior. Negative reinforcement can be very effective. You have also seen it's power everyday – think about when you get into the driver's seat and forget to put on your seatbelt. The annoying alarm (verbal or beeping) will remind you to put on the seatbelt and often continues if you don't. What do you do when you hear the alarm. You don't get a reward, but you do get the alarm to turn off. This alarm is a great example of negative reinforcement. In practice management, negative reinforcement can be used to change behavior without having to provide monetary compensation. For example, distribute among all your physicians a weekly report of incomplete documentation (number of cases that are incomplete and have not been billed). You will easily see that each physician does not want their name on the list. Similarly, if the group is receiving incentive payments from the hospital to meet turnover time goals, publishing daily a turnover report and including the anesthesiologist's name can make meeting turnover time important to every member of your group.

Omission. Goal: To decrease frequency of *undesirable* behavior by removing all "reinforcing behavior". Three steps to Omission: (1) identify the behavior to be reduced or eliminated, (2) identify the reinforcer that maintains the behavior, and (3) stopping the reinforcer. The best example of omission is on-time meeting start. (1) The behavior to be eliminated is showing up late for a group meeting. (2) The reinforcer is waiting for people to show up to start. (3) Start the meeting at the time scheduled.

Punishment. Goal: To decrease frequency of *undesirable* behavior. Punishment should be reserved as a last resort and only in cases of serious behavior. To be effective, the punishment needs to be linked directly to the undesired behavior, immediate in feedback, and appropriate for the behavior. The reason punishment should be used sparingly is that there are potential short-term and long-term negative effects to the employee being punished as well as other employees including apathy, high turnover or absenteeism, and aggressive or disruptive behavior. Further "learned helplessness" can occur with punishment.(7)

Reassessment of Behavior Modification System. Unlike the simple model, the more complex model reflects that periodic reassessment of the effectiveness of the behavior modification system is essential. If the problem is solved (increase in the desired behavior or decrease in the undesired behavior), then continue with the system unchanged. If it is not solved, then reassess the behavior identified, the method of measuring the behavior, and the reinforcements are correct or need to be changed.

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Table 1: Confounding Factors or Anesthesia-Independent Factors

	Surgery	Anesthesia Time (hr)	Turnover (min)	# cases done	Base/case (total billed)	TU/case (total billed)	(total tASA billed)
OR 1	Lap Chole (fast)	1	20	7	7 (49)	4 (28)	(77)
OR 2	Lap Chole (slow)	2	20	4	7 (28)	8 (32)	(60)
OR 3	CABG	2.5	30	3	20 (60)	10 (30)	(90)
OR 4	Lap Chole (golf)	2	20	2	7 (14)	8 (16)	(30)
L&D	Labor Epidural	6	n/a	3	5 (15)	4 (12)	(27)

Hypothetical OR suite and labor and delivery (L&D). The anesthesiology group staffs the anesthetizing sites from 7:30 AM to 4:30 PM. Confounding factors affect billed units can be seen by comparing billed units for different ORs: surgical duration (OR 1 and 2), type of surgery (OR 1, 3), schedule "not full" or downtime (OR 2 and 4), and obstetric anesthesia (L&D and OR 2 and 4). For OR 4, the surgeon must leave at noon and hence no cases are available to be done after this time. For labor epidural, only "face-to-face" time billed, i.e. 1-hour for 6-hour epidural analgesia. See text for details.
OR = operating room; base = base units; TU= time units; tASA = total ASA units; lap chole = laproscopic cholecystectomy; CABG = coronary artery bypass graft.

Figure 1: Simple Behavior Modification System

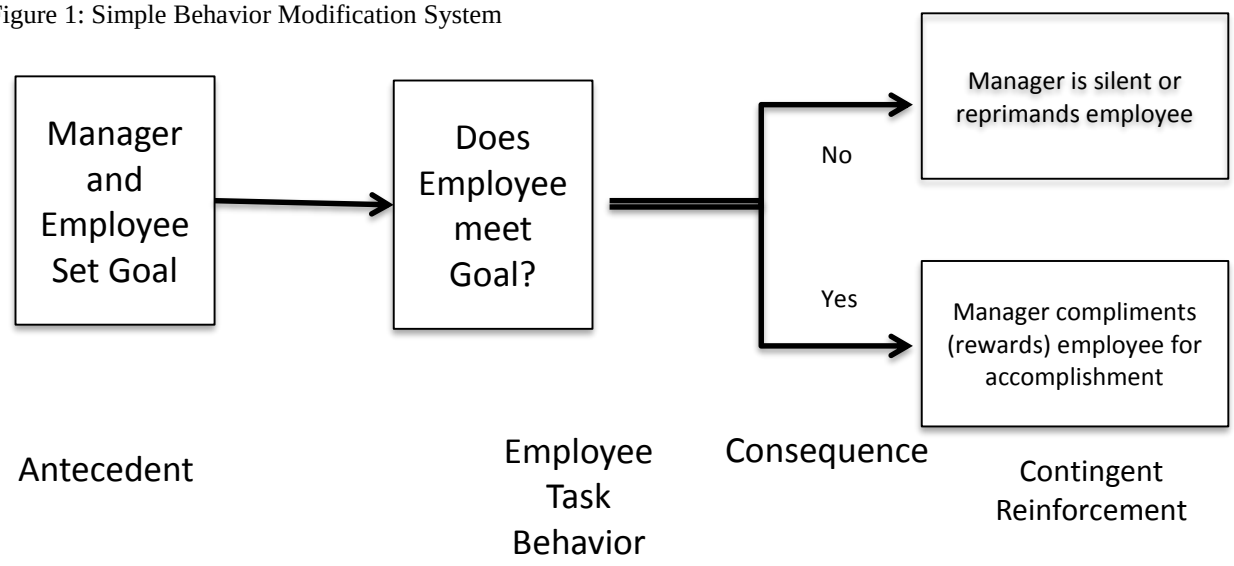
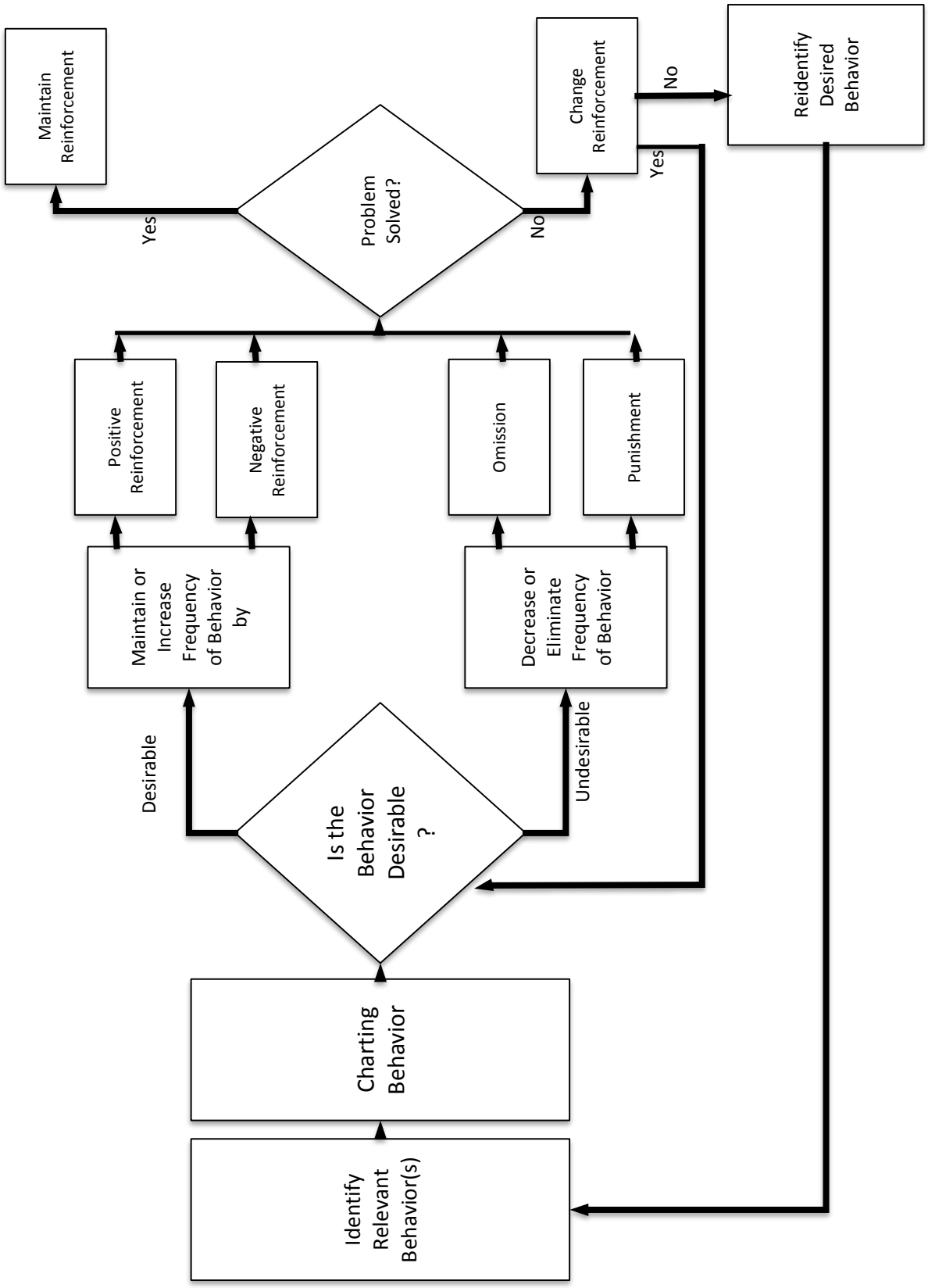


Figure 2: Behavior Modification Systems more than "Simply Setting Goals"
Adapted from Figure 4.6 (Reference 5)



ANESTHESIOLOGY 2017
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Chronic pain and substance abuse: anesthesia management techniques

David M. Dickerson, MD **Chicago, IL**

Introduction

Patients living with chronic pain or substance use disorder present unique and specific challenges for the ambulatory anesthetist. These biopsychosocial diseases impact perception through maladaptive neurophysiologic changes in the brain. High quality care of these complex patients requires clinician awareness and preparedness.

Chronic pain: epidemiology

Nineteen percent of European adults reported suffering pain multiple times a week in the preceding 6 months.[1] Several socio-demographic factors are associated with chronic pain: female gender, older age, lower socio-economic status, geographical and cultural background, employment status and occupational factors, and history of abuse or interpersonal violence.[2] Pain affects more Americans than diabetes, heart disease and cancer combined.[3] This prevalence has significant relevance to the anesthetist as preoperative pain is a significant predictor of postoperative pain intensity.[4]

Chronic pain: anesthetic considerations

Caring for the patient with chronic pain in the outpatient center presents several challenges. Some patients with chronic pain may be opioid tolerant or dependent further increasing their complexity and pain care needs. Chronic pain even in the absence of opioid dependence is associated with increased postoperative pain.[4] The central nervous system of patients with chronic pain is primed for aberrant nociceptive processing. The loss of protective endogenous analgesic mechanisms and upregulation of pro-nociceptive processes result in accentuated pain experience postoperatively.

Chronic pain in the ambulatory setting

Ambulatory surgical care creates value for patients, surgeons, health systems, and payers, a value derived from high quality, cost-effective patient throughput. Outpatient surgery emphasizes rapid anesthesia and surgical recovery with postoperative care taking place primarily at home with the help of informal caregivers that include family and friends. Patients with chronic pain may find significant challenges in rapid transition to home-based, independent recovery unless motivated to do so. Such motivation requires patient preparation and treatment planning. In the absence of such care planning and discussion, these patients are at risk for unanticipated admission, delayed discharge, decreased satisfaction, and poor quality of recovery.

Preoperative opioid use

Preoperative opioid use is associated with increased cost, risk and poor outcomes.[5,6] Preoperative opioid tapering may improve postoperative outcomes.[7] Applying robust nonopioid analgesia and avoidance of techniques that induce hyperalgesia enable optimal quality of recovery. Table 1 details therapies that improve postoperative pain for patients with or without opioid tolerance.[8]

Challenges in postoperative care

Postoperatively, opioid requirements may increase 100-200% after surgical injury. Such doses may be outside of the standard prescribing practice of surgeons and may require coordination and planning with the patient's primary prescriber. In the event such doses are prescribed, the surgical group utilizes standard practices set forth by the 2016 CDC guidelines for safe opioid prescribing.[9] The use of treatment contracts, close follow up, education as to risks and goals of the therapy, and the plan for discontinuation and disposal of therapy compose a best practice for all opioid prescriptions, but most importantly for doses of opioids greater than 50mg daily oral morphine equivalent, in patients with substance abuse history, lung or renal disease, obesity, advanced age, or on concurrent benzodiazepines. Effective pain management through regional anesthesia and non-opioid based techniques attenuates opioid consumption, and as a result, the degree of potential opioid escalation postoperatively.

Addiction and substance use disorder: epidemiology

"Substances" are psychoactive compounds with the potential to cause health and social problems. Misuse is defined as consumption that can cause harm to the individual or those around them. As defined by the American Society of Addiction Medicine, addiction is a chronic disease of brain reward, motivation, memory and related circuitry. The individual suffering from addiction pathologically compulsively pursues reward or relief via substance use and other behaviors with diminished recognition of the self-harm incurred in the pursuit. The chronicity of the disease manifests as episodes of recurrence and remission. Like other chronic diseases, the majority of patients suffering from addiction have a genetic predisposition.

Millions of Americans use or misuse alcohol, illicit drugs, over-the counter drugs or other substances such as inhalants and solvents. Amongst Americans aged 12 or older, 66.7 million individuals admitted to binge drinking in the past month and 27.1 million individuals admitted to using an illicit substance.[10]

Addiction and substance use disorder: anesthetic considerations

When actively misusing or abusing illicit substances or prescription medication, patients are at increased risk for medication interactions and adverse perioperative events. End-organ dysfunction can occur in substance users. Acute intoxication can increase or decrease levels of anesthetic or analgesic requirements and is substance specific. The preoperative history and physical examination can identify potential acute intoxication, ongoing substance use, and any physiologic impact of acute or chronic use.

Acute intoxication on day of surgery

Addiction impacts cognitive functions such as insight and judgment, potentially jeopardizing preoperative preparations or adherence to instructions.[11] Addiction associated cravings are profound and potentially exacerbated by stress. Dose up titration by the patient on the day of surgery due to concerns for inadequate pain or anxiety management can result in somnolence or toxicity preoperatively. The somnolent or intoxicated patient raises alarm and triggers in depth medication and social history, physical examination, and possible urine toxicology testing. Such evaluation is undertaken with family or friends present only if the patient consents to discuss highly confidential medical information with them present. A non-confrontational approach enables collaboration and strengthens the doctor patient relationship. A positive urine toxicology screen may not necessarily reflect acute intoxication but rather, recent use. Clinical assessment delineates risk. Candid conversation, emphasizing the potential risk of undergoing surgery while intoxicated enables shared decision making and creates an environment conducive to full disclosure by patients and clinicians.

Substance abuse history and postoperative outcomes

Patient history of substance abuse or misuse complicates anesthetic care. In 2015, 20.8 million people aged 12 or older met criteria for a substance use disorder.[10] History of substance use creates significant challenge for the anesthetist and ambulatory surgical center on the day of care and during surgical recovery. Postoperative opioid overdose is rare yet substance abuse history is the strongest predictor of opioid overdose in hospitalized patients (Odds ratio = 14.8; 95% confidence interval: 12.7-17.2).[12] Validated tools for risk stratification for opioid related respiratory depression may help in the decision to defer a patient's surgical care to a hospital-based setting.[13]

Medication-assisted treatment: Full and partial opioid agonists and opioid antagonists

In the absence of treatment, opioid use disorder is a life threatening illness. Medication-assisted treatment (MAT) leads to better treatment outcomes compared to behavioral treatments alone.[10] Methadone, buprenorphine, and naltrexone are the most commonly prescribed medications for MAT. While reducing cravings and relapse risk, and overdose related death, these medications are associated with increased pain postoperatively due to opioid tolerance (methadone) or active competitive opioid receptor antagonism (buprenorphine, naltrexone). Patients taking these medications are identified preoperatively to permit adequate treatment planning. The surgical visit identifies such patients at time of procedural selection.

Medication-assisted treatment: stop or continue prior to surgery?

Continuing or stopping MAT perioperatively creates distinct challenges for the ambulatory surgical team. Such management is led by the patient's prescribing physician in concert with the anesthesia and surgical groups and with the patient's consent. Patients are offered regional anesthesia techniques with a continuous approach when feasible while limiting opioids due to concern for lack of effect or risk of increasing relapse potential. Supplementing care with comprehensive multimodal analgesia improves pain while sparing opioids. Table 1 details a myriad of non-opioid, analgesic options. Postoperatively, the patient's psychologist, psychiatrist or primary physician monitors for signs of misuse or relapse via frequent follow up.

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Table 1. Established perioperative non-opioid therapies for the patient with chronic pain or addiction issues

Care Phase	Preoperative (Day of surgery)	Intraoperative	Postoperative (*Discontinued prior to discharge)
Pharmacologic Agents	Gabapentin/pregabalin		Gabapentin/pregabalin
	Nonsteroidal anti-inflammatory drugs (NSAIDS)		
	Acetaminophen		
		Lidocaine infusion*	
		Ketamine infusion*	
	Regional anesthesia, single shot or continuous catheter		
	Intravenous dexamethasone		
		Infiltrative local anesthesia	
		Dexmedetomidine infusion	
		Esmolol infusion	

ANESTHESIOLOGY 2017
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Obesity and OSA: It's More than Just a Bad Airway

Rainer Lenhardt **Louisville, Kentucky**

Epidemiology and Pathophysiology of Obesity

Over the past 20 years obesity has become a true epidemic worldwide.[1] The latest OECD (Organisation for Economic Co-operation and Development) report showed an obesity rate of 38.2% in the United States.[2] Interestingly enough, the prevalence of obesity did not change between 2003 and 2012.[3] By definition of the World Health Organization, obesity starts at a body mass index (BMI) of ≥ 30 kg/m^2 and is further broken down into three classes: class I (30-34.99 kg/m^2), class II (35- 39.99 kg/m^2), and class III (≥ 40 kg/m^2), which is called morbid obesity (MO).[4] When confronted with greater BMIs, the term super-obese is used for those with a BMI of 50 to 69.9 kg/m^2 and hyper-obese for patients with a BMI > 70 kg/m^2.

Obesity is a chronic inflammatory and metabolic disease affecting all organ systems.[5] Hence, morbidity is increased in this patient population rendering surgery more likely than in non-obese patients. As an example, obese patients are more prone to endometrial, breast, colo-rectal, prostate, or renal cancer and a variety of benign surgical conditions such as cholecystitis, uterine adenoma or ovarian cysts, just to name a few. In addition, obesity claims 26 to 55 million quality-adjusted life years.

As surgical procedures are rising in the obese patient population, anesthesiologists are increasingly challenged by obese patients' co-morbid conditions that especially affect the cardio-vascular system and the respiratory system. In addition, obese patients tend to have a greater prevalence of difficult airway and obstructive sleep apnea.

Obesity leads to an increase in metabolic demand and, thus, to an augmentation in cardiac output. Cardiac output and stroke volume rise proportionally to body weight. Because of an increased cardiac workload, left ventricular hypertrophy can ensue. In addition, pulmonary blood flow is increased and can result in pulmonary hypertension with eventual right heart failure.[6] Overall, obese patients are more prone to cardiomyopathy, heart failure, myocardial infarction, pulmonary embolism and "sudden death."[7]

Extra weight causes extra pressure on the thorax reducing the functional residual capacity (FRC) significantly. A reduced FRC leads to less oxygen in the lungs after induction causing early hypoxia due to a diminished oxygen reserve. Extra pressure on the thorax also reduces thorax and lung compliance. Additionally, it increases airway pressures during positive pressure ventilation with an increased risk of barotrauma, particularly during laparoscopic procedures in Trendelenburg position.

Many obese patients suffer from excess fatty tissue in the pharyngo-laryngeal and nuchal region. Excess tissue can obstruct the airway, rendering mask ventilation and intubation potentially difficult. There is, however, some controversy in the literature regarding difficult intubation in the obese compared to the non-obese patient.[8] Obesity is related to obstructive sleep apnea (OSA) and, in extreme cases, can lead to obesity hypoventilation syndrome (OHS). Both OSA and OHS can cause postoperative hypoxia due to hypopnea/apnea that can go undiagnosed if only monitored by pulse oximetry.

Lastly, obesity is highly linked to metabolic syndrome. Metabolic syndrome is a combination of altered insulin resistance and impaired glucose tolerance, hyperlipidemia, and hypertension with central obesity. Central obesity is defined as obesity with a waist to hip ratio of ≥ 0.9 in males and ≥ 0.8 in females.

Preoperative Assessment of the Obese Patient

The American Heart Association (AHA) and the American College of Cardiology (ACC) have developed guidelines for the evaluation of patients undergoing non-cardiac surgery.[9] These guidelines can be used for obese and non-obese patients alike. The main emphasis is on the evaluation of the functional capacity of the obese patient along with potential risk factors such as history of congestive heart failure, heart disease, cerebrovascular disease, diabetes, and chronic renal failure. While the history may be obtained fairly easily, it may be difficult to assess functional capacity for reasons other than cardiac dysfunction. In this case the AHA/ACC recommends a 12-lead ECG to detect signs of cardiomyopathy such as left bundle branch block, left axis deviation, right bundle branch block, and right axis deviation as signs of pulmonary hypertension and right heart failure. If three or more risk factors are present, it may be prudent to perform a stress-echocardiography to evaluate ejection fraction and right heart functional status.

Functional capacity may be restricted by respiratory dysfunction. Respiratory assessment is advisable in the obese patient, starting with auscultation and pulse oximetry. In addition, a simple spirometry can be helpful. The Society for Obesity and Bariatric Anesthesia (SOBA) recommends a pre-operative blood gas analysis if 1) arterial saturation is lower than 95%, 2) forced vital capacity is below 3 liters, 3) serum bicarbonate concentration is higher than 27 mmol/l, or 4) there is wheezing at rest.[10]

Anesthesiologists may be confronted with a difficult airway in the obese patient. An observational report of over 170,000 patients found that a BMI of ≥ 30 kg/m^2 was an independent risk factor for both difficult mask ventilation and difficult intubation.[11] A large neck circumference is a useful additional indicator and, when greater than 60 cm, is associated with a 35% probability of difficult laryngoscopy.[12] Patients with known OSA and patients with a STOP- Bang score of three or higher are at increased risk for having a difficult airway.[13] More specifically, OSA has been shown to be a risk factor for difficult intubation in obese patients.[14]

Obesity and OSA are closely linked. The incidence of OSA was reported to be as high as 80% in patients undergoing bariatric surgery and is proportional to BMI.[15,16] OSA is an independent risk factor for perioperative complications ranging from re-intubation, prolonged intubation, and assisted ventilation to irreversible hypoxia and brain death.[17]

It is recommended to screen obese patients for OSA. The STOP-Bang questionnaire was developed to screen patients for OSA and is valid for obese patients. [18] This questionnaire contains questions about the presence of snoring, tiredness during daytime, observed apnea during sleep, hypertension, elevated BMI, age, neck-circumference, and gender. A score of five or greater has shown a good correlation with the severity of OSA and postoperative apnea.[19]

Perioperative Management

After appropriate preoperative screening and risk assessment of the obese patient a decision should be made as to if the patient is suitable for complex ambulatory surgery. Patients with severe cardiac and /or pulmonary co-morbidities should be admitted to the hospital and monitored on the floor or in a step down unit. Obese patients with tolerable risks can be scheduled as outpatients, if the surgical procedure is suitable. Thus, the right selection of obese patients for ambulatory surgery is of paramount importance. A systematic review showed that BMI alone is not associated with an increase in perioperative complications or unplanned admissions after ambulatory surgery.[20]

In an ideal ambulatory setting, obese patients should be treated with regional anesthesia and minimal sedation. The key is to avoid airway manipulation and general anesthesia including the use of opioids. If the obese patient needs a secured airway, the patient should be placed in a ramp position, so that the tragus of the ear is at the level of the sternum. Preoperative continuous positive airway pressure (CPAP) lengthens post-induction nonhypoxic apnea time and is recommended in obese patients with OSA. [21] Additional airway equipment including video-laryngoscopy and malleable stylets should be available for intubation.

During general anesthesia opioid consumption should be held at a minimum. Recently, opioid-free anesthesia has been advocated in obese patients. Opiod-free anesthesia includes dexmedetomidine, ketamine, lidocaine infusions, acetaminophen, NSAIDS, along with regional anesthesia. [22] Repeated alveolar recruitment maneuvers may improve intraoperative oxygenation and reduce airway pressures.[23] On emergence, the obese patient should be fully reversed, breathing adequate tidal volumes, positioned in reverse Trendelenburg position, and fully awake before extubation.

Obese patients, in particular when suffering from OSA, greatly profit from postoperative CPAP or BIPAP management. If patients are using a CPAP machine at home, they should bring it with them for the postoperative period.[24] In obese patients who are in need of opioids for pain control, CPAP treatment early after surgery may improve OSA and ameliorate the respiratory-depressant effects of opioids without undue hemodynamic effects.[25]

Previously undiagnosed patients with a STOP-Bang score of five or greater should also be treated with non-invasive pressure support. Monitoring of end-tidal CO_2 and respiratory rate can help to detect apnea or hypopnea episodes early on. In case of such episodes, a patient should not be discharged home and monitoring should continue over night.

In summary, the obese patient may be suitable for ambulatory surgery if treatment of cardiac and respiratory co-morbidities is optimized, and if the surgery is non-complex and short. Ambulatory surgery must not increase or alter the perioperative risk compared to inpatient surgery. Perioperative risks typically occur at induction and during general anesthesia, as well as in the early postoperative period. In any event, an individual discussion with the obese patient and the surgeon should be encouraged in a pre-admission testing clinic before an ultimate decision is made to plan for ambulatory surgery. Close monitoring after surgery is warranted. If the patient is hemodynamically stable, has an oxygen saturation of pre-anesthesia values without supplemental oxygen, a normal respiration rate, and no apnea or hypopnea episodes, the obese patient should be allowed to be discharged home.[10] It is mandatory, that the patient will be accompanied by a family member or friend over night.

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Providing Safe Care and Improving Outcomes for Complex Ambulatory Surgery Patients

Cardiac and Pulmonary Cautions: Aortic Stenosis, Pulmonary Hypertension, and More

Sher-Lu Pai, M.D. **Jacksonville/ Florida**

Introduction

As the field of ambulatory anesthesiology continues to expand, the push to perform anesthesia on patients with cardiac diseases in the outpatient setting has increased. Safety and quality of care for these complex patients poses challenges for all ambulatory anesthesiologists. From preoperative evaluation, preoperative medical optimization, patient selection, availability of resources and information handoffs, each step of the patient care process plays an important role in the success of providing safe anesthesia to patients with major cardiac and pulmonary conditions in the ambulatory setting.

Not only will this refresher course discuss the physiologic alterations and medical management of patients with commonly known complex conditions, such as aortic stenosis and pulmonary hypertension; it will also discuss the risk management of complex patients in this unique practice setting. Proper management of these conditions may increase the capacity of an ambulatory surgery center.

Different Settings of Ambulatory Surgery Centers

Understanding what resources are available may assist in scheduling patients appropriately. Appropriate resources and trained personnel must be readily available for adverse events.

Categories of ambulatory surgery:

1) Ambulatory surgery center adjacent to a hospital with supporting resources from the hospital, such as blood bank, interventional cardiology and other specialty consultations.
2) Freestanding ambulatory surgery center remote from a hospital with paucity of support.
3) Office-based procedures with very limited support.

Functional Capacity

Functional status is a reliable predictor of perioperative and long-term cardiac events.[1] Even in patients with major comorbidities, such as cardiac failure, ischemic heart disease and chronic obstructive pulmonary disease; higher preoperative functional capacity is still associated with lower surgical complications, hospital lengths of stay, hospital readmissions and overall health care costs.[2-4] Patients with moderate or better functional capacity (≥ 4 metabolic equivalents) can generally proceed to surgery without additional preoperative cardiovascular testing.[1]

Patient Selection

Seven independent risk factors were identified for perioperative morbidity: overweight or obese body mass index, chronic obstructive pulmonary disease, history of transient ischemic attack or stroke, hypertension, previous cardiac surgical intervention and prolonged operative time.[5] Decompensated and poorly stabilized cardiac and respiratory patients are at high-risk for complications.[6]

Patients with stable cardiac and pulmonary comorbidities may be considered for ambulatory surgery. By identifying the patient who is at risk prior to surgery, we could optimize the patient's preoperative health status through medical intervention and appropriate perioperative care which may reduce risks and morbidity and mortality, specifically for the sicker patients at higher risk.[7] When assessing risk, it is also important to consider

other factors impacting patient outcomes, such as the patient's clinical status, the skill of the surgeon and anesthetist, surgical and anesthetic technique and the ambulatory surgery setting.[6] The goal is to prevent perioperative exacerbation of the patient's cardiac or pulmonary disease.

Unanticipated Admission after Ambulatory Surgery

Unanticipated admissions are more frequent after ear, nose and throat procedures and urologic ambulatory procedures. Regardless of the type of surgical procedure performed, patients who present with prolonged surgical duration, a high American Society of Anesthesiologists physical status classification (≥ 3), an increased body mass index, cardiac disease and advanced age (≥ 80 year-old), have an increased risk of unanticipated admission.[8, 9]

Management of Cardiac Conditions

Hypertension (HTN) and Coronary Artery Disease (CAD)

Preoperative evaluation of the patient with HTN should assess if there is an adequate control of blood pressure and whether there is a presence of end-organ damage. Uncontrolled HTN may warrant a consult for effective antihypertensive treatment prior to ambulatory surgery. Ambulatory surgical patients should continue their prescription β-blockers[1], α-2 agonists[10, 11] and calcium channel blockers[12, 13] on the day of the surgery. The risks and benefits of continuing angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy in the perioperative period have been debated. Data on the continuation is limited to observational analysis. Some evidence showed that patients who continued ACE inhibitors or ARBs on the day of surgery had more transient intraoperative hypotension, but no increase in cardiovascular adverse outcomes, such as death, stroke or myocardial infarction.[1, 14] In patients with CAD and hyperlipidemia, lipid management is an important step in preventing the formation of atherosclerosis. Statins are the most commonly used agents and have the benefit of not only correcting lipid abnormalities, but also possessing anti-inflammatory properties that improve the overall environment of the arterial endothelium.[15, 16] It should be continued in the perioperative setting.

If newly onset or unstable angina is present, the patient needs to be referred for cardiac evaluation and optimization prior to ambulatory surgery. Proper preoperative evaluation may allow early preoperative therapeutic interventions of CAD. If the patient had a recent myocardial infarction, ambulatory surgery may only be considered at least 30 days after the infarct while the patient's functional status returns and angina symptoms have resolved.[1, 17] However, these patients may not be best suited for ambulatory centers lacking immediate access to interventional cardiology. CAD patients who have undergone percutaneous coronary intervention with coronary stents are subjects to stent thrombosis and antiplatelet therapy. It has been recommended to delay elective noncardiac surgery by at least 30 days for bare-metal stents and more than 1 year for drug-eluting stents after implantation in patients on dual antiplatelet therapy [1]. However, patients with recent stent placement may only be suited for ambulatory centers with immediate access to interventional cardiology.[18]

Aortic Stenosis (AS)

The AS patient with symptoms or with a valve area < 1 cm^2 or mean transvalvular pressure > 40 mmHg is at risk of perioperative mortality and nonfatal myocardial infarction.[19, 20] A patient with severe AS is not recommended for surgery in an ambulatory setting. However, preoperative assessment with available echocardiogram permits proper planning of perioperative care in asymptomatic patients with less severe stenosis, allowing the specific patient population to safely undergo ambulatory surgeries. Undiagnosed stenosis may be hazardous in the ambulatory surgical setting as anesthetic techniques and intraoperative management may reduce preload and cardiac output drastically, resulting in cardiopulmonary collapse.

Heart failure (HF)

Although some studies showed a higher mortality rate of HF patients after surgery regardless of procedure urgency, [21] elective procedures should not be performed in patients with new onset or decompensated HF.

Pulmonary hypertension (PH)

PH is a progressive disease of multiple etiologies and different severity. Patients who present to preoperative evaluation with suspected or confirmed PH should have a comprehensive evaluation and treatment for

medical optimization prior to surgery. A complete medical history and physical examination with assessment of functional capacity and cardiac function is necessary.[22] PH patients with serial echocardiogram and EKGs without symptoms may be suitable for an ambulatory surgical procedure with low cardiac risk. Serial cardiopulmonary exercise testing and the 6 minute walk test may provide further assessment of exercise tolerance.[22] Patients with a history of PH should continue all preoperative pulmonary vasodilator therapies throughout the perioperative period.[23] Clear communication between teams, adequate preoperative assessment with clear understanding of the severity of the disease and perioperative anesthetic techniques to maintain an adequate systemic vascular resistance and adequate preload may ensure patient safety.[22] The availability of immediate resources, such as inhaled nitric oxide and a specialty consult, may also determine the feasibility of performing ambulatory procedures in this specific patient population.

Management of Pulmonary Conditions

Chronic Obstructive Pulmonary Disease (COPD) and asthma are reactive airway diseases associated with increased perioperative complications.[5] Smokers and patients with asthma have 2- to 5-fold higher risk of developing perioperative respiratory events in ambulatory surgical centers.[24] Ambulatory patients with these pulmonary conditions should receive adequate control of airway hyperreactivity prior to surgery. The usage of β2-agonists, leukotriene antagonists, or steroids and the frequency of recent exacerbations provide the information on the severity of the disease. Patients are to continue their pulmonary medications throughout the perioperative period. If available, a preoperative pulmonary function test with and without bronchodilators may determine the reversibility of the obstruction in COPD patients. Smoking cessation is highly recommended. Smoking causes sputum production with chronic changes in lung function, bronchial reactivity and ciliary dysfunction.[25] Although 4 weeks is required to reduce the incidence of perioperative complications [26, 27], all patients should be encouraged to discontinue smoking regardless of the timing related to the surgery as short-term abstinence from tobacco does not increase the risk of complications after surgery.[28, 29]

Summary

To remain competitive and economically viable, the field of ambulatory anesthesiology has to expand its practice to include patients with medical comorbidities while providing safe care and improving patient outcomes. Complex ambulatory surgery patients need thorough, timely and team-based preoperative evaluations with proper information hand-offs to the anesthesiologists providing perioperative care. Optimizing comorbidities prior to surgery is a crucial initial step in minimizing risk. Complete knowledge of the existing complex medical conditions and preparedness for these conditions in the perioperative setting is also crucial to keep the patients safe in the ambulatory setting.

Disclosure

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Diabetes and Neurologic Conditions: Medications Matter

Refresher Course Panel: Providing Safer Care and Improving Outcomes for the Complex Ambulatory Surgery Patient

Mary Ann Vann MD **Boston, MA**

Introduction

There are similarities between two very different conditions which require special attention to the perioperative management of medications during ambulatory surgical procedures. These two conditions are Diabetes and Parkinson's disease. Patients with both these diseases also benefit from special attention to scheduling their time of surgery. Diabetes patients should be placed as the first case of the day. Parkinson's Disease patients are optimally scheduled around their medication dosing. In both cases, the scheduling of their ambulatory surgical procedures should aim to maintain the patient's usual medications at the usual times. Each medical condition will be discussed individually in the following text.

Diabetes

Diabetes affects 29.1 million people in the US. However 25% of these patients do not know they have the disease.[1] The ADA[2] classifies the disease into the following categories: Type 1 diabetes is caused by the autoimmune destruction of β-cells which leaves the patient with an absolute insulin deficiency, so they require daily insulin to survive. The ADA this year renamed this condition "Immune-Mediated Diabetes." Only 5% of all diabetic patients have Type 1. Type 2 diabetes begins as insulin resistance, which manifests as a relative insulin deficiency after a progressive loss of adequate β-cell insulin secretion. Sufficient insulin is produced by most type 2 patients to cover basal needs and prevent ketosis.

A major problem with perioperative management of ambulatory surgical patients with diabetes is treating them all alike, instead of recognizing the differences in treatment of the diseases and in the patient's ability to self-manage. All patients with diabetes should be asked about their comfort and skill in managing their diabetes prior to giving any preoperative instructions.[3] Disease specific questioning includes the duration and type of diabetes, adherence to medications, level of glycemic control, and frequency of self-monitoring of blood glucose(BG). Patients on complicated insulin regimens are most able to handle changes in their medications, test themselves frequently, and treat themselves appropriately for high or low blood glucose. Glycemic control reflected in HbA1c levels can reflect the ability of a patient to manage their diabetes.

Often an anesthesiologist's fear of perioperative hypoglycemia in a fasting ambulatory surgical patient hinders optimal glucose control, and subject a patient to perioperative complications related to high blood glucose which includes infections. While there are many reasons for perioperative hyperglycemia, a common one is inappropriate discontinuation of a patient's usual medication.[4] The practitioner should ascertain the incidence and frequency of hypoglycemia, the blood glucose at which symptoms occur or presence of hypoglycemia unawareness.

Hypoglycemia is a common occurrence in Type 1 diabetes patients and advanced Type 2 patients. Elderly patients are at increased risk for hypoglycemia due to fewer symptoms and diminished counter regulatory responses.[5] The alert value for hypoglycemia is BG<70 mg/dL,[2] which allows time for a response prior to symptoms in well controlled patients. A new designation by the ADA is "Clinically significant hypoglycemia" which is BG <54 mg/dL and is sufficiently low to indicate serious, clinically important hypoglycemia. Finally The ADA no longer

designates a specific glucose value as severe hypoglycemia, but describes it as hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery.

The thresholds for hypoglycemic symptoms are dynamic, reduced by frequent low BG values and elevated by poor glycemic control. Type 1 patients in good control average two symptomatic hypoglycemic episodes each week and spend 10% of the time with BG of 50-60mg/dl.[6] Beta cell failure in Type 1 diabetes impairs glucagon and epinephrine release in response to low BG while this is preserved in most Type 2 patients. Often patients with Type 1 diabetes in good control have hypoglycemia unawareness. These patients should be encouraged to check their BG frequently while fasting, and utilize their continuous glucose monitors (CGM) during the perioperative period.

The usual treatment for hypoglycemia is 15-20gm of glucose or other simple sugar. For a fasting patient this is best accomplished with 4-8 ounces of a clear juice or sugary drink. Glucose gels or tablets are not recommended as they may be particulate.[3,4] For a patient with an IV, 250cc of D5W or 25cc of D50 provides 12.5gm of dextrose. BG should be measured 15 minutes after treatment, additional glucose administration may be required as hypoglycemia may persist. An ambulatory surgical patient with diabetes should travel to and from the facility with testing supplies and treatments for hyperglycemia.

Oral and Injectable Medications for Type 2 Diabetes

Nearly 75% of diabetes patients take oral hypoglycemic drugs.[1] Metformin is the first line oral hypoglycemic. Metformin is a biguanide drug which sensitizes a patient to their own insulin. A risk of lactic acidosis exists for patients with renal insufficiency, and metformin is often held prior to radiologic procedures requiring contrast. The ADA advises holding metformin for 24 hours before surgery.[2] Thiazolidinediones are also sensitizers and have been associated with heart failure. Insulin secretagogue drugs, sulfonylureas including glinides, and meglitinides may cause perioperative hypoglycemia. Sulfonylureas pose the greatest risk of hypoglycemia, especially when combined with other treatments.[7]

Incretins are the intestinal hormones which increase insulin production and decrease glucose production with food intake. Drugs with incretin like effects comprise two categories of Type 2 diabetes treatments. The dipeptidyl peptidase-4 (DPP 4) inhibitors include the drugs sitagliptin, saxagliptin, inagliptin and alogliptin. Glucagon like peptide -1 (GLP-1) receptor agonists are incretin mimetics and include the injectable drugs exanatide, lisaglutide, dulaglutide and albiglutide. Some of these drugs are only injected once per week, so they take a long time to achieve therapeutic levels and can have effects on a patient several weeks after discontinuation. These once weekly injections however, have fewer side effects than the daily doses. The main adverse effects are delayed gastric emptying, nausea and diarrhea. Attention to these drugs have increased since several studies have shown two drugs in this category can reduce cardiovascular mortality in type 2 diabetes patients with known cardiac disease.[7] Another injectable drug for Type 2 diabetes is the amylin analog Pramlinitide which is taken with meals as it is meant to delay gastric emptying and blunts the pancreatic secretion of glucagon.[2] All these injectable drugs have a small risk of hypoglycemia when combined with sulfonylurea drugs or insulin. However, there are new medications which combine long acting basal insulins and GLP-1 agonists in a single injection.[2,7]

The newest category of oral antidiabetes drugs is sodium glucose cotransporter 2 (SGLT-2) receptor inhibitors which work in the kidney to increase excretion of glucose. These new drugs are canagliflozin, dapagliflozin and empagliflozin and are administered orally once daily. While there has been no evidence of perioperative risk to these drugs, there is a risk of euglycemic diabetic ketoacidosis in both type 1 and type 2 diabetes patients receiving these medications.[2] It is postulated that prolonged preoperative fasting and surgical procedures may put patients at increased risk of this ketoacidosis.[2] Also these drugs may cause volume depletion, orthostatic hypotension and urinary tract infections. These drugs are often utilized in combination with other categories of antidiabetes drugs. The SGLT-2 inhibitor empagliflozin had also been shown to reduce the risk of cardiovascular death in diabetes patients with known heart disease.[7]

Perioperative Management of Oral and Injectable medication:

Oral antidiabetic medications and non-insulin injectables should be held on the day of surgery, and may be taken again once normal food intake resumes. ADA recommends holding metformin for 24 hours prior to surgery.

Insulin Therapies

While only 5% of adult patients have Type 1, almost 29% of diabetes patients take insulin.[1] The preferred regimen for Type 1 diabetes is physiologic insulin dosing (also called basal-bolus), which mimics endogenous insulin production by providing basal, prandial or nutritional, and correction doses.[2] Continuous subcutaneous insulin infusions (CSII) via an insulin pump or long-acting peakless insulin analogs are utilized for basal dosing. Basal insulin comprises approximately 50% of the patient's total daily dose (TDD) of insulin and covers basic metabolic needs so should not cause hypoglycemia. Patients administer variable boluses of rapid acting nutritional insulin to match the carbohydrate content of meals. The final element of a physiologic insulin regimen is for correction of elevated BG with the same insulin used for nutritional dosing.

The peakless basal insulins are similar in that they are slowly absorbed from the subcutaneous injection site. Glargine is longer acting than Detemir. Glargine is usually administered once per day in Type 1 patients and once or twice per day for Type 2 patients. Detemir is administered once or twice a day. The newest long acting peakless insulin is Degludec. It's duration of action is greater than 24 hours and may last as long as 32-40 hours. Degludec may also be found mixed with rapid acting insulin aspart in a 70/30 or 55/45 ratio.[2]

While there are some Type 2 patients who take physiologic insulin, most utilize peakless basal insulin alone or intermediate acting or pre-mixed insulins.[2] For these patients the peakless insulin supplements oral medications and endogenous insulin production, and may cause hypoglycemia while fasting. Type 2 diabetes patients are insulin resistant and usually require higher insulin doses for the same level of BG control. Administration of pre-mixed or fixed combinations of intermediate and short or rapid acting insulins poses a challenge perioperatively since each component should be dosed separately while NPO. Both components of premixed NPH and regular insulin are available alone, but for Humalog Mix, intermediate acting lispro protamine is not offered as a single agent, so NPH must be substituted. The most commonly used premixed insulins include NPH/Regular 70/30, 70/30 aspart mix, or 72/25 or 50/50 lispro mix. These premixed insulins may be administered 1-3 times per day.[2] Split dosing of one component of these premixed insulins will usually have to occur at the facility. Premixed insulins are associated with more hypoglycemia than peakless basal insulins.[2]

As part of the preoperative evaluation, the type, brand and dose of insulin should be documented. On the day of surgery, it is desirable for the patient to bring their own insulin with them.[3] Insulin potency can vary greatly with the time it has been open, and the method of storage. It is advisable to give the patient their own insulin to get a predictable effect, and also many centers will not stock the patient's brand or type of insulin.

Over 20% of Type 1 diabetes patients in the U.S. utilize insulin pumps. The pump will deliver a continuous basal infusion of a rapid acting insulin analog (RAIA), lispro, aspart, or glulisine, and adjustable nutritional and correction insulin boluses. Pump programming allows multiple basal rates to match diurnal rhythms and activity level. The lowest basal rate should be used during the perioperative period, some advocate reducing this by 10-20% to prevent hypoglycemia.[8] Basal insulin is vital for metabolic functions, so replacement insulin must be administered if the pump is discontinued. An insulin deficient patient's BG will rise 45mg/dL per hour if basal insulin is withheld.[9] Most pumps have 3 elements: the insertion site (needle or cannula inserted subcutaneously), tubing, and programmable pump with internal insulin reservoir and battery.

Perioperative Management of Insulin for Ambulatory Surgical Patients

Day before surgery: Patients may take usual insulin doses on the day prior to surgery unless they experience nocturnal hypoglycemia, whereby they may reduce bedtime or evening insulin doses. Basal insulin dosing should be maintained provided it is only 50% of TDD (and part of a physiologic regimen with a RAIA)[3] or reduced to 60-80% of usual.[2] Insulin pumps should deliver usual sleep or sick day basal rates. For type 2 patients on peakless basal insulin only, bedtime doses may be reduced or omitted. NPH insulin given at dinnertime can be continued, as the peak occurs prior to sleep. Doses of NPH insulin at bedtime may be reduced or omitted if the patient reports hypoglycemia if breakfast is delayed.

Day of surgery: Patients on a physiologic insulin regimen may take usual dose[3] or reduce their peakless basal insulin to 60-80%[2] on the morning of surgery. Peakless insulin given solely (usually Type 2 patients) should be held or reduced as calculated from the dosing interval and predicted or actual time of fasting.[3,10] Early arrival and management at the facility is recommended for patients taking intermediate-acting insulin preparations. For brief early morning cases, NPH or sole peakless insulin can be held until after the procedure. For longer procedures, or later in the day, the sole basal or intermediate insulin can be reduced. This formula is applicable to pre-mixed or fixed-combination insulins, but only pertains to the intermediate acting component. The formula utilizes the dosing interval, and the predicted or actual time of fast to calculate the percentage of the insulin dose the patient should receive while NPO. It subtracts the time of the fast from the hours of the dosing interval and divides that number by the dosing interval to achieve the fraction of insulin dose to cover that period.[10]

Correction doses of insulin: During the perioperative period, it is recommended to administer rapid acting insulin analogs subcutaneously for correction dosing.[2,3,4] This allows a fairly quick reduction of blood glucose with short duration of action so patients can be observed until peak effect has passed. Subcutaneous insulin is easy to administer, avoids large swings in blood glucose, and duplicates the patient's normal routine. Hypoglycemia may occur from overlapping or "stacking" repeat doses of rapid acting insulin analogs. Subcutaneous insulin absorption occurs fastest from the abdomen, followed by arms, thighs, and buttocks but is affected by perfusion, heat and cold.[3]

There are several methods for determining the appropriate correction dose: empirical, utilizing the patient's usual correction factor, or calculations based on the patient's TDD of insulin via the "rule of 1800/1500" formula, which predicts the decrease in blood glucose expected after 1U of rapid acting insulin based on a patient's insulin sensitivity as reflected by the total daily dose of insulin.[3,10]

Insulin Pumps: An insulin pump can continue during general anesthesia with certain safeguards.[8,11] Some authors recommend limiting pump use to cases lasting less than one or two hours. The infusion site and tubing must be secured away from the surgical field. Isolating the pump itself from direct patient contact and shielding from X-rays minimizes potential interference. All wireless features should be disabled to minimize electrical interference; this includes any continuous glucose monitor communication with the insulin pump. Checking the BG every hour will ensure proper pump function. Subcutaneous correction doses of RAIA should be given by syringe, not from the pump. It is advisable for any facility that allows insulin pumps to have a standardized perioperative insulin pump checklist and/or protocol.

Parkinson's Disease

Parkinson's disease (PD) is a neurologic disorder which most often affects elderly patients, and is more common in males. It is characterized by muscle rigidity, tremor at rest, bradykinesia and postural instability resulting in a gait disturbance.[12,13,14] The symptoms of PD are due to a reduced level of dopamine activity in the basal ganglia, specifically the substantia nigra. The lower levels of dopamine cause enhanced excitatory effects of acetylcholine (ACh). The difficulty in treating PD is that there is not a straightforward or easy method to increase dopamine levels in the brain without causing adverse effects in the periphery. PD patients also have non motor manifestations such as cognitive impairment, sleep disruption and autonomic dysfunction resulting in dysphagia, gastroparesis and orthostatic hypotension.[13] The leading cause of death in PD patients is aspiration pneumonia.[12]

While there are currently many different medications used to treat patients with PD, one medication is the mainstay of treatment.[12] This first line medication is a combination of levodopa and carbidopa. This preparation is only available in oral form. The reason for the combination is to decrease the adverse effects of levodopa conversion to dopamine in the periphery, the most common of which is dyskinesia. The carbidopa inhibits decarboxylating enzymes in the periphery and allows more of the levodopa to cross the blood brain barrier and be converted to dopamine there. Negative effects of higher levodopa doses include decreased myocardial norepinephrine stores, peripheral vasoconstriction with reduced intravascular volume, which combined with autonomic dysfunction causes orthostatic hypotension. Many drugs commonly administered during anesthesia may increase the PD patient's symptoms including fentanyl, metoclopramide and haloperidol.

The levodopa/carbidopa combination drug has a relatively short time of effect and variability in blood levels due to gastric absorption disturbances common in PD.[13.14] As a rule patients need more of the drug over time with decreasing times between doses.[15] Also, patients are usually on time schedules not dosing schedules (e.g. q6), as they require their medications at specific times of day.[12] Any time the PD patient is not at a therapeutic level, their ability to function is diminished. This need for adherence to the patient's levodopa/carbidopa dosing schedule is an issue for the perioperative period. Weakness and chest wall rigidity can impair ventilation after a delay in dosing of 6-12 hours. Weakness can also inhibit swallowing (since dysphagia is very common) and increase the PD patient's already elevated aspiration risk. Also their suitability for discharge home after ambulatory procedures can be questionable if not in optimal condition, as PD patients are at a higher risk of falls than similarly aged patients.[12] Thus it is very important to try to maintain the patient's usual dosing schedule in the perioperative period, to allow a PD patient to return home successfully after ambulatory surgery. The patient should receive his scheduled doses prior to surgery and any missed dose immediately after surgery. Also note that oral levodopa/carbidopa should be taken on an empty stomach, one hour before meals or two hours after meals.[16] Neuropathy in PD patients has also been attributed to levodopa/carbidopa drugs. [17]

PD patients who are not satisfactorily treated with standard oral levodopa/carbidopa due to tight dosing schedules, unpredictable gastric absorption and emptying, or inability to swallow pills, may be switched to a newer formulation of levodopa/carbidopa which has recently been approved for use in the US.[18] This is a suspension of levodopa/carbidopa in an intestinal gel which is infused into the jejunum via a percutaneous endoscopic gastrostomy tube with a jejunal extension (PEG-J). The patient is given a morning bolus plus a continuous maintenance infusion lasting approximately 16 hours, and has the ability to give themselves an extra bolus when needed to treat symptoms.[14,19] A majority of patients who receive this treatment have seen decreases in their required daily doses of levodopa/carbidopa with improvement in quality of life with more time without PD symptoms and less dyskinesia.[14,18] The most common adverse events associated with this treatment are problems with the PEG-J.19 Management of these PD patients in the perioperative period could be difficult, with need for specific instructions on dosing and time of discontinuation of the infusion. If the infusion must be discontinued for a length of time, there should be consideration of neurologic consult to switch the patient to an oral regimen.[17]

In the case of a PD patient missing doses of their levodopa/carbidopa there are two rapid acting solutions. One is an orally dissolving form of levodopa/carbidopa, which can be administered even if the patient cannot swallow.[12,18] The other medication which can be administered in the case of a patient with acute symptoms of weakness is apomorphine. Apomorphine is a dopamine receptor agonist with a rapid onset and offset which is administered subcutaneously.[15] There are no opioid analgesic properties to this drug. The reason for the subcutaneous route is to avoid first pass hepatic metabolism and avoid renal toxicity. The duration of a 2mg subcutaneous dose is .58 hours, and a total dose of 4mg is usually effective for most patients and lasts .72 hours. Side effects of apomorphine are nausea and vomiting, and hypotension.[12] However, it is very unlikely that an ambulatory facility would stock this drug. For many reasons, patients with PD should be carefully evaluated for appropriateness for a free standing ambulatory facility.

A rare complication of rapid discontinuation of levodopa/carbidopa is Parkinson Hyperpyrexia syndrome which is similar in presentation to neuroleptic malignant syndrome.[12] When this syndrome occurs, the patient may present with altered mental status, rigidity, fevers and autonomic dysfunction.

Occasionally, a patient with mild early PD may be on a drug other than levodopa/carbidopa. However, levodopa/carbidopa is the gold standard drug for most patients. Additional drugs are usually given to patients who have more severe PD, unable to be managed with levodopa/carbidopa alone, or who have significant dyskinesia or other side effects. The number and type of drugs a patient is receiving should be considered when evaluating and selecting PD patients for ambulatory procedures.

Other dopamine agonists utilized to treat PD include pramipexole, ropinirole and the rotigotine patch, which being a transdermal route delivery, can be maintained during the perioperative period or used as a bridge when other medications are held.[12] Some PD patients are taking MAO-B inhibitors including Selegine and Rasagilene. Similar to other MAOI, they should be discontinued 1-2 weeks before surgery. Catechol-O-methyltransferase (COMT) inhibitors such as entacapone and tolcapone decrease the breakdown of dopamine in the brain, and are used as an adjunct treatment in PD. Another means of treatment to improve PD symptoms is by restoring the balance between dopamine and ACh by utilizing anticholinergics such as benztropine and trihexphenidyl or the cholinesterase inhibitor rivastigmine. Amantadine may be administered to PD patients to reduce the incidence of dyskinesia from levodopa/carbidopa therapy.[16] Since all these drugs are not usually the primary treatment of PD, doses can be missed without great effect.

Conclusion

There are interesting similarities between the Type 1 diabetes and the PD patients. Both require their basal medications to be continued during the perioperative period and those medications are most effective when given to simulate normal physiology. The difference in perioperative outcome however can be significantly different. The PD patient can experience acute deterioration and hindrance of basic life functions including ventilation and ambulation without their medication. The diabetic patient's outcome certainly may be poorer without good perioperative glucose control, but only hypoglycemia, which is easily diagnosed and treated, is an acute situation. Simple steps can prevent hypoglycemia without increasing the effects of hyperglycemia. Most ambulatory surgical facilities will not be prepared to improve the effects of a PD patient with severe symptoms due to discontinuation of their medication so proper patient selection is mandatory.

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ANESTHESIOLOGY 2017
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Sedation Versus General Anesthesia for Endovascular Treatment

W. Andrew Kofke, M.D., M.B.A.. **Hospital of the University of PA, Philadelphia, PA.**

Endovascular Thrombectomy for Ischemic Stroke(ETIS) has become a standard of care for patients presenting with acute ischemic stroke1. Initial data supported ETIS within 6 hours of presentation but more recent reports support ETIS up to 24 hours after presentation but with concerns about higher blood pressure associating with hemorrhagic complications2. Experts uniformly support the notion that hospital systems and process are extremely important and with 2 million neurons a minute dying supports the slogan that time is brain3. Also important are physiologic variables during and after the ETIS1.

Retrospective evaluation of the ETIS studies generally agreed that general anesthesia(GA), without a definition of what constitutes GA, is associated with worse clinical outcome after ETIS4. Retrospective studies also generally indicated that the process was slowed when GA was used and blood pressure was lower. Notably, there was a paucity of anesthesia-based authors in these retrospective ETIS reports.

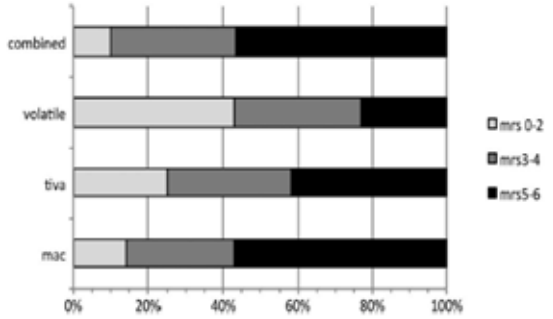

Fig 1. Outcome metrics. % of patients with modified Rankin Scale (mRS) scores at discharge derived from the medical record according to type of anesthesia. Scores were better in the group receiving volatile anesthesia after induction of anesthesia($P<0.05$). From Sivasankar etal with permission

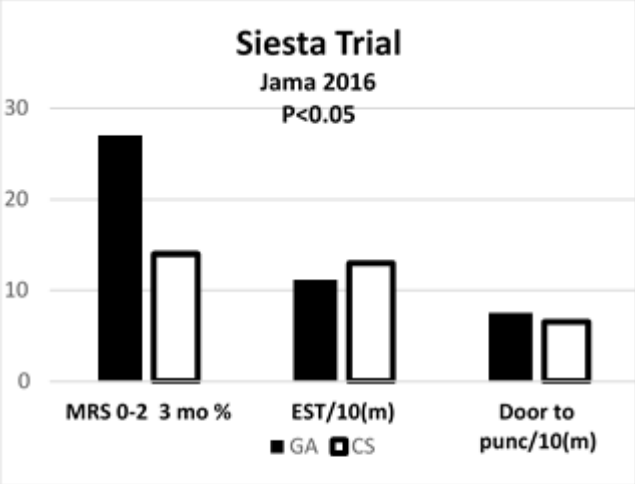

Fig 2. 3 mos mRS for functional independence (0-2) better for GA (P=0.01), endovascular stroke treatment time(EST) shorter with GA ((P=0.04), and door to fem puncture time longer with GA (P=0.03). Data from Schonenberger,2016

This situation has led to a handful of studies performed by anesthesiologists. Sivasankar etal5, in a retrospective single institution study involving mostly GA patients, reported better outcomes in patients receiving volatile anesthesia. These patients had excellent physiologic support in contradistinction to the concerns of stroke neurologists in prior reports. Presently this is the only study comparing types of anesthetics. This is somewhat unexpected as a subhuman primate study of focal temporary ischemia by Selman etal6 indicated significant neuroprotection with barbiturates. The observations may be explained by a report of Hofman etal7 showing better brain pO2 during focal ischemia in humans with desflurane compared to barbiturates. Several RCTs have recently been published. The SIESTA trial8 compared GA with conscious sedation (CS) finding no difference in clinical outcomes between the techniques acutely although the 3-month mRS scores trended to better in the GA group (fig 2). The GA group had a higher incidence of hypothermia, delayed extubation, and 3 month mortality with a shorter procedure time but longer door to puncture time.. Notably this study was done without anesthesiologists and the specific drugs employed were not included in the final report in JAMA. Two subsequent studies the ANSTROKE9 and GOLIATH10, 11 studies, have recently been reported. The ANSTROKE study compared GA with profofol induction and maintenance with sevoflurane and remifentanil with remifentanil CS. No difference between groups was observed. In contrast the GOLIATH trial, comparing GA with remifentanil/propofol with fentanyl propofol CS observed improved MR measures of infarct size and clinical measures with mRS in the GA patients. There is another larger study ongoing in China, the CANVAS study which will compare GA with remifentanil/propofol titrated to BIS 40-60 with propofol titrated to BIS >70. This study will be the first one to consider a measure of depth of anesthesia and sedation and will have a larger sample size, projected to enroll 640 patients.

In conclusion, presently RCT data seem to modestly favor GA with intravenous anesthesia although a retrospective study favors volatile anesthesia. However, studies are not well controlled for actual pharmacodynamic and pharmacokinetic factors as it is possible for a CS to adjust to a relatively deep level of anesthesia as conditions may dictate, whereas intubated neurologically depressed patients may require lower anesthetic doses. It is also important to consider system issues regarding continuous availability of skilled anesthesiologists and their capability to integrate into a system oriented to rapid induction of anesthesia and beginning of the procedure.

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Is That All There Is? ICU Management of Acute Stroke

Martin Smith MBBS FRCA FFICM **London, United Kingdom**

A more aggressive approach to the management of acute ischemic stroke (AIS), including endovascular interventions and decompressive craniectomy, has resulted in increasing numbers of patients being admitted to intensive care units.[1] In addition to monitoring and managing intracranial complications, critical care focuses on blood pressure and glucose optimization, avoidance of fever and hypoxia/hyperoxia, fluid and nutritional optimization, and early integration of rehabilitation strategies.[2] In the absence of high quality evidence, management strategies have been developed with expert consensus.[3;4]

Monitoring

In the awake and cooperative patient, regular neurological examination and cranial imaging are the cornerstones of detecting deterioration after AIS, and remain the focus of clinical decision-making.[1] Hypodensity involving greater than 50% of the middle cerebral artery (MCA) territory or worsening midline shift on computed tomography (CT) imaging are highly predictive of the development of malignant MCA syndrome.[5] ICP monitoring is often used in patients with large space-occupying infarcts and edema, but measured ICP values may be normal despite large ischemic tissue volumes.[6] Multimodality neuromonitoring-guided management has potential, but unproven, benefit after AIS.[1] Because the majority of stroke patients are not sedated, non-invasive neuromonitoring techniques might have wider applicability but none are sufficiently reliable for routine clinical use.[7]

Optimizing systemic physiology

Optimization of systemic physiology is central to the critical care management of stroke patients.

Hypoxemia, airway protection and mechanical ventilation

Hypoxemia is common after AIS and adversely affects outcome. It has multiple causes including aspiration, pneumonia, pulmonary embolus, neurogenic or cardiogenic pulmonary edema, acute lung injury, and central respiratory arrhythmias. Controlled trials have failed to demonstrate clinical benefit of routine oxygen supplementation after AIS,[8] and oxygen therapy is only indicated in self-ventilating patients if SpO_2 falls below 95%.[1]

There are several indications for mechanical ventilation including reduced conscious level and pre-existing or stroke-related respiratory complications. The mortality rate of intubated and ventilated stroke patients is variously reported to lie between 40% and 80%, but most studies are old and include small patient cohorts.[9] Given the recent major changes in stroke management and associated improved outcomes, current mortality rates of ventilated patients are likely lower. Between 15% and 35% of intubated stroke patients require tracheostomy because of severe bulbar palsies or a requirement for prolonged mechanical ventilation.[9] Potential benefits of tracheostomy include decreased risk of pneumonia,[10] reduced ICU length of stay, patient comfort and improved ability to communicate. In the SETPOINT randomized pilot trial of 60 patients with ischemic or hemorrhagic stroke, early tracheostomy (1–3 days) did not reduce ICU length of stay compared to standard tracheostomy care (7–14 days), but was associated with lower ICU (10% vs. 47%) and 6-month (27% vs. 60%) mortality.[11] It is generally recommended that the need for tracheostomy in stroke patients be assessed one week after institution of mechanical ventilation.[9]

Cardiovascular management

There is a U-shaped relationship between blood pressure (BP) and outcomes after AIS.[12] Extreme hypertension may result in encephalopathy, hemorrhagic transformation of infarcted tissue and cardiac complications, whereas low BP can decrease perfusion to the penumbral region and worsen cerebral ischemic injury. More than 75% of patients are hypertensive within the first 24 hours of stroke onset,[13] but the acute management of elevated BP remains controversial.[14] Acute BP lowering has been associated with adverse, neutral and positive effects on stroke outcomes,[15] and is therefore not recommended as a routine unless there are specific indications for urgent treatment such as myocardial ischemia, aortic dissection, heart failure or hypertensive encephalopathy.[16] The 2013 AHA/ASA Stroke guidelines recommend that BP should be treated only when systolic and diastolic BP exceed 220 mm Hg and 120 mm Hg respectively except in patients receiving thrombolysis or endovascular therapy when BP should be

lower than 185/110 mmHg before commencement of treatment and for 24 hours thereafter.[4] Given the concern that aggressive BP lowering can be detrimental, a reasonable approach is to reduce BP initially by 15% to 25% over 24 h while monitoring for neurological deterioration. There is no evidence to guide which agents should be used to manage hypertension after AIS, but short-acting drugs such as labetalol appear to be safe.[17] While early use of angiotensin receptor antagonists may reduce post-stroke cardiovascular events, there is no evidence that this benefit is related to BP reduction and some evidence of harm from the angiotensin-receptor blocker candesartan.[18] Patients taking chronic anti-hypertensive medication should resume oral treatment once they are medically stable and as soon as they can swallow medication safely, although there is no urgency in most cases to re-start therapy in the first days after stroke.[19]

There are theoretical arguments for elevating BP after AIS to increase blood flow to the ischemic penumbra, but there have been only a few small clinical trials with inconclusive results.[20] Many questions remain about the safety and potential benefits of pressor therapy and it is currently not recommended except in certain sub-groups of stroke patients, such as those with severe carotid stenosis.[21]

In addition to absolute pressure, BP variability in the first few hours and days after AIS has been associated with a higher risk of 90-day mortality and worse functional outcome.[22] These associations are strongest in patients with lower mean BP and proximal vessel occlusion, and persist after recanalization therapies.[23] On the other hand, some studies have found no association between BP variability and stroke outcomes.[24] Because of the dynamic nature of BP after AIS, frequent monitoring should be undertaken and continuous monitoring via an arterial line is recommended in patients with unstable or variable BP.[1]

Cardiac problems are common in stroke patients, either as a stroke trigger (e.g. cardioembolic event) or as a consequence of it.[1] Dysrhythmias are reported in more than 50%, elevated cardiac troponin in up to 20%, and abnormal left ventricular function in around 12% of patients.[25] A history of cardiovascular disease may predispose to sudden death after AIS; this is believed to result from interaction between cardiovascular and neurologic pathology related to impaired central autonomic control, or involvement of the insular cortex which may directly lead to cardiac damage and arrhythmias.[26] All critically ill stroke patients should undergo continuous EKG monitoring and have an echocardiogram which should be repeated if abnormal ventricular function is identified.

Fluid management

Fluid balance should be carefully monitored and managed to maintain euvolemia. Dysphagia is common after hemispheric and brainstem strokes and, in the absence of a safe swallow, patients should receive intravenous fluids and be considered for nasogastric feeding within 24 hours.[27] Consensus guidelines recommend 0.9% saline for intravenous fluid replacement with avoidance of dextrose-containing solutions except in the presence of hypoglycemia.[4] Daily fluid replacement should be individualized based on the patient's ideal body weight, clinical status and comorbidities, rather than administered as a fixed volume per day.[1]

Blood glucose management

Hyperglycemia occurs in 30-40% of stroke patients, most commonly as a result of an acute stress response rather than pre-existing diabetes.[28] Hyperglycemia is associated with a range of deleterious effects including larger infarct volumes, susceptibility to infection, and worse clinical outcomes. In one observational study there was a threefold increase in 3-month mortality and poor functional outcomes in patients with blood glucose $\geq$155 mg/dL anytime during the first 48 hours after AIS compared with those who were normoglycemic.[29] The adverse effects of hyperglycemia are particularly evident after cortical infarction, in non-diabetic patients and those with persistently elevated blood glucose.[30] Compared with normoglycemic patients, the relative risk of in-hospital or 30-day mortality is 3.3 and 2.0 in non-diabetic and diabetic stroke patients respectively who are hyperglycemic at hospital admission.[31] This increased risk is independent of other predictors of poor outcome.

Although regular blood glucose monitoring and meticulous glycemic control is essential after AIS, optimal treatment targets and methods of glucose control remain a matter of debate. Tight glycemic control has not been shown to improve outcomes[32] and, although, several studies have highlighted the risk of hypoglycemia with aggressive lowering of blood glucose this has not been associated with adverse outcomes.[33] Most clinical studies have been conducted in stroke units using subcutaneous administration of insulin for glucose management, and it is

not clear whether their findings can be translated to the ICU where glycemic control with insulin infusion control is routinely undertaken and well monitored. The multicenter SHINE study will randomize 1400 hyperglycemic stroke patients to assess the effect on 90-day functional outcome in patients receiving IV insulin to maintain glucose concentration between 80-130 mg/dL compared to standard care to maintain glucose < 180 mg/dL.[34] Current AHA/ASA guidelines recommend maintaining blood glucose between 140–180 mg/dL early after AIS.[4] While hypoglycemia (blood glucose < 60 mg/dL) should always be prevented or promptly treated, overcorrection must be avoided because excessive glucose reperfusion may worsen neurologic injury.[35]

Temperature control

Pyrexia develops in up to 50% of stroke patients and is independently associated with poor outcome.[36] A meta-analysis of six cohort studies including 2,986 patients found that temperature ≥ 37.4°C within the first 24 hours of admission was associated with twice the mortality compared to that of afebrile patients.[37] The multicenter double-blind PAIS randomized controlled trial of 1500 stroke patients with admission temperature between 36˚C and 39˚C found that empirical high-dose (6 g/day) acetaminophen administered within 12 hours of stroke onset did not improve overall outcomes compared to placebo, but suggested potential benefit in those with admission temperatures between 37˚C and 39˚C.[38] However, the subsequent PAIS 2 study found that routine administration of acetaminophen to patients with temperature between 37˚C and 39˚C did not improve outcome, although it was terminated after only 256 of a planned 1500 patients were recruited.[39] Based on limited or low quality evidence, recently updated European guidance does not recommend routine prevention of hyperthermia with antipyretics as a means to improve functional outcome and/or survival after AIS, and is unable to make any recommendation for the treatment of hyperthermia.[40]

Preclinical studies confirm a neuroprotective role of therapeutic hypothermia (TH) after AIS,[41] but this has not translated into benefit in clinical studies.[42] A Cochrane systematic review found no overall benefit or harm from TH after AIS, although a clinically significant effect could not be ruled out because of the substantial heterogeneity of included studies.[43] Future studies should standardize temperature targets, hypothermia induction methods, time windows for initiation of TH and duration of treatment, and use of adjuvant therapy. TH has substantial side-effects include shivering, electrolyte disturbance, impaired renal function, impaired cardiac function, and immunosuppression.[44] In a small study in conscious stroke patients, surface cooling to 35.0°C, but not to 34.5°C or 34.0°C, was feasible, but cooling to any degree was associated with an increased risk of pneumonia.[45]

Anemia

Anemia (defined as hemoglobin <12 g/dl in women and <13 g/dl in men) has been reported in more than 95% of stroke patients on the ICU,[46] and low and further decreasing hemoglobin concentration is independently associated with 3-month mortality and poor outcome.[47] The adverse effects of anemia may be related to stroke severity; in one study low haemoglobin concentration was independently associated with outcome in less but not more severe strokes.[48] Evidence from general critical care suggests hemoglobin concentration ≥ 7 g/dl is the optimal threshold for red cell transfusion in the absence of serious cardiac disease, but the sensitivity of the injured brain to oxygen deprivation suggests that similar thresholds might not be applicable in stroke patients.[49] On the basis of mathematical modelling, hemoglobin concentration of 10 g/dl has been proposed as a rational red cell transfusion trigger after AIS,[50] but robust clinical evidence to support this is lacking. Although anemia should be avoided, aggressive transfusion strategies are not currently recommended because of the risks of red cell transfusion and lack of evidence of benefit.[49]

Management of intracranial complications

The major intracranial complications following AIS are the development of intracerebral hemorrhage and cerebral edema causing mass effect.

Hemorrhagic transformation

Symptomatic hemorrhagic transformation occurs in 5-6% of patients undergoing intravenous thrombolysis and intra-arterial recanalization strategies, but can also occur in the absence of reperfusion therapy. It is more common after intra-arterial compared to intravenous thrombolysis, most likely because of the use of anticoagulation and antiplatelet therapy to reduce the risk of thrombus formation related to intra-procedural catheter and stent use.[51] There is no robust evidence to guide treatment of AIS-related intracranial hemorrhage, but key management points

include timely diagnosis and prevention of hematoma expansion by strict BP control and reversal of thrombolytics.[2] Cryoprecipitate, fresh frozen plasma, and recombinant factor VII may be considered in severe cases, but there is no evidence to support their routine use or to guide discontinuation of antiplatelet therapy. Maintenance of SBP<160 mmHg in patients with sizable or symptomatic hemorrhagic transformation seems a reasonable option.[33] The decision to offer surgical evacuation should be determined by the size and location of the hemorrhage as well as the patient's overall clinical condition. Evacuation of large hematomas may be lifesaving, whereas deeper, smaller hemorrhages are best managed conservatively and monitored with serial imaging.

Cerebral edema

Clinically significant cerebral edema develops in a small but significant proportion of patients with AIS, typically those with occlusions of the internal carotid artery, MCA, or both. Treatment options for malignant MCA infarction include general measures to limit space-occupying edema, but these are often ineffective.[52] Osmotherapy does not improve outcomes,[5] and steroids have no role.[53] A number of small studies have demonstrated the safety and feasibility of moderate hypothermia to control ICP after AIS, but potential beneficial effects on outcome remain unproven.[40]

The benefits of decompressive craniectomy in malignant MCA infarction in patients aged between 18 and 60 years are well-established. In a pre-planned merged analysis of three trials including 93 patients in whom treatment was initiated within 48 h of stroke onset, hemicraniectomy significantly reduced12-month mortality compared to conservative management (22% vs. 71% respectively; absolute risk reduction 50%) and also resulted in a higher proportion of patients with favorable outcomes.[54] The effect of surgery was highly consistent across the three trials, and there was no difference in the benefits of surgery for any of the predefined subgroup analyses including age (older or younger than 50 years), presence or absence of aphasia, and earlier time to treatment (randomization before or later than 24 h after stroke onset). A Cochrane systematic review confirmed these findings, but cautioned that an overestimation of effect size could not be excluded because all trials were stopped early.[55] Compared to standard care, decompressive craniectomy also reduces mortality after MCA infarction in stroke patients aged over 61 years (33% *vs.* 70%) although surgery is associated with a substantially increased proportion of severely disabled survivors in this age group.[56] Decisions to recommend decompressive craniectomy must therefore be made not only in the context of its clinical indications but also after consideration of an individual patient's preferences and quality of life expectations.

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ANESTHESIOLOGY 2017
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Practical Pediatric Regional Anesthesia

Santhanam Suresh, MD **Chicago, IL**

Introduction: Regional anesthesia is experiencing rapid growth in pediatric anesthesia. The use of ultrasound guidance has increased the variety for blocks that can be performed in infants, children and adolescents. The increased safety of performing blocks with US guidance has allowed the practitioner to attempt to perform more difficult blocks compared to previously described using landmark techniques.[1-4] The use of ultrasound guidance can also allow minimal use of local anesthetic solutions thereby decreasing the risk of toxicity.[5] In this lecture, a variety of regional anesthesia techniques will be described that you can use in your everyday practice. Central neuraxial as well as peripheral nerve blocks will be described with clinical techniques as well as images for reference while performing these blocks.

Equipment: As the field of regional anesthesia is exploding, the use of ultrasound imaging is undergoing constant improvement. Several ultrasound imaging machines with the capability of offering a variety of applications including echocardiography have entered the market with greater emphasis on user-friendliness and portability. This may be of greater importance in the pediatric population since most of these blocks are performed in the operating room under general anesthesia. In children, it may be easier to perform regional anesthesia with deep sedation or under general anesthesia.[6] Recent multi-center reports demonstrate regional anesthesia under general anesthesia is safe in children[7]. US probes commonly used in children include a high frequency hockey stick probe and a linear 25 mm high frequency probe. Since most of the neurovascular structures are located superficially in children, visualization of neural structures is easier with a high frequency probe. The physics and equipment descriptions can be found in textbooks on US guided regional anesthesia. US guidance can be used for central neuraxial blocks as well as for peripheral nerve blocks. A brief description of each of these blocks will be provided at this refresher course. In general, the use of curvilinear probes is limited to the use in older children and obese individuals.

Central neuraxial blocks:

Epidural Analgesia:
Ultrasound imaging seems promising for use either pre-procedurally (prior to puncture) or during block performance (US aided), although the latter may be most suitable in infants. The largely cartilaginous posterior vertebral column of neonates and infants enables good US beam penetration to view the spinal structures and can in some cases enable a view of the needle tip trajectory. Acceptable safety of neuraxial catheters in neonates has been demonstrated.[8]

Epidural Analgesia:
- US-guided technique does not preclude continuous testing for loss of resistance.
- The limitation of the technique is that the needle shaft and tip may be hard to localize with the tangential relationship of the needle (midline) and the probe (paramedian longitudinal).
- An assistant (2nd set of hands) is required during catheter placement in order to perform the imaging real-time for US aided catheter placement. It is important to use saline for LOR to facilitate US imaging.

Techniques
Sonoanatomy:
A moderate-high frequency probe (hockey stick, 13-6 frequency probe) is utilized using a paramedian longitudinal view. The 'window' between the two spinous processes will allow the operator to visualize the anterior complex (anterior duramater, and the posterior longitudinal ligament), the posterior duramater and the ligamentum flavum. Our preference is to visualize the neuraxis using a paramedian approach. In a paramedian longitudinal view at the thoracic spine, the spinous processes are represented by slanted hyperechoic lines beneath the homogeneous-appearing paravertebral muscle mass. Dorsal shadowing will be apparent deep to the spinous processes and other posterior vertebral elements. The highly hyperechogenic ligamentum flavum and dura mater are captured lying in the alternate 'windows', and the underlying spinal cord appears largely hypoechoic with an outer bright covering of the pia and a central line of hyperechogenicity (median sulcus).[2] In the first report of US imaging in central blockade, Chawathe et al. performed a pilot study in 12 patients (1 day old to 13 months) to evaluate the possibility of detecting catheters, and verifying their placement, within the epidural space after placement (within 24 hours) via the direct lumbar route.[9] The important point from this paper is that US imaging (specifically using the midline approach) of static structures such as catheters can be performed, yet only reliably in very young patients where much of the posterior bony elements of the spinal column may exist as cartilage, thus allowing good US beam penetration. An optimal angle of probe alignment needs to be evaluated in children and surrogate markers for viewing needle and catheters may be necessary to facilitate a dynamic technique. Willschke et al placed epidural catheters under real-time US guidance using the paramedian longitudinal imaging plane in 35 neonates.[10] Needle tip entry and the injection of local anesthetic solution within the epidural space were used to confirm epidural placement; these parameters could be viewed in all neonates. Epidural catheters could only be identified via surrogacy through tissue movement (i.e., anterior movement of the duramater) and fluid injection.

Caudal Needle Placement

- Initially use a transverse plane of imaging to identify the sacral hiatus located between the cornua; the sacral hiatus is located between an upper hyperechoic line representing the sacrococcygeal membrane/ligament and an inferior hyperechoic line representing the dorsum of the pelvic surface (base) of the sacrum.
- Rotate the probe to the longitudinal plane (a paramedian plane may be required in older children) to capture the sacrococcygeal membrane, a relatively thick linear hyperechoic band, sloping caudally.
- Insert the needle under either plane of view, although a longitudinal view may allow for optimal viewing along the needle. A transverse view can be used after needle placement within the epidural space, in order to view the spread of local anesthetic solution (as dilation of the caudal space and localized turbulence).

Caudal Epidural Block
Caudal blocks, including both single-shot caudal and lumbar or thoracic epidural catheters advanced from the caudal epidural space (thus avoiding the spinal cord), is a commonly practiced regional anesthesia technique in children. Although this technique is practiced with the identification of landmarks, there is a small, but not insignificant chance for failure.

Sonoantomy: Ultrasound imaging at the midline using both transverse and longitudinal alignment of the probe should be performed prior to needle placement in order to appreciate the patient's anatomy and to identify the sacrococcygeal ligament, dural sac and cauda equina. A linear high-frequency small footprint or hockey stick probe is a suitable choice, although a larger footprint may be used when viewing the longitudinal axis to allow an adequate field of view. Placing the probe initially in a transverse plane at the coccyx and scanning in a cephalad direction can help with landmark identification particularly during training in sonoanatomy. This view allows a good delineation of the sacral hiatus; the sacral cornea are viewed laterally (as "humps") and the sacral hiatus is located between an upper hyperechoic line representing the sacrococcygeal membrane/ligament and an inferior hyperechoic line representing the dorsum of the pelvic surface (base) of the sacrum. Placing the probe longitudinally between the sacral cornua will capture the dorsal surface of the sacrum, the dorsal aspect of the pelvic surface of the sacrum and the sacrococcygeal ligament. The sacrococcygeal ligament covers the sacral base beyond the end of the dorsum of the sacrum. It appears as a relatively thick linear hyperechoic band, sloping caudally. The sacral hiatus is identified as a hypoechoic space located between the dorsum of the sacrum and the dorsal side of the pelvic surface of the sacrum. In older patients where the structures may be ossified at the midline, the paramedian longitudinal view may be necessary since it will allow the US beam to penetrate the spaces on either side of the spinous processes. This paramedian view would allow appreciation of the ventral movement of the duramater during fluid injection, but would not allow a real-time view of the needle along its axis.

Technique: During or after skin puncture with the needle, both transverse and longitudinal sonographic planes can be used for confirming caudal epidural needle placement. Roberts at al. published a prospective observational study of 60 children, in which they determined whether a saline test bolus could be reliably imaged with US in order to confirm cannula placement in the caudal epidural space.[11] While transverse imaging was performed in the pre-puncture scan to help visualize the neuraxial structures (there was no mention of measurements or skin markings), longitudinal imaging (approximately 1 cm above the cannula insertion site) was used during the saline test bolus of 0.2-0.3 ml kg^{-1} to view the anterior displacement of the posterior duramater. The longitudinal plane may allow a view of the long axis of the needle as it penetrates the sacrococcygeal ligament. This technique may be particularly beneficial to allow adjustments in needle angle to ensure adequate length of advancement and depth of penetration without intraosseous placement. The optimal angle for needle insertion during caudal block has been evaluated using US, since many of the previous recommendations include multiple angles, necessitating needle manipulations, including a steep initial angle, which may increase the incidence of bony puncture. When introducing a catheter into the caudal space to reach the lumbar or thoracic spine, similar technique to the above is used for cannula placement and the catheter is viewed during advancement using US imaging at the level of the spine above the sacrum. The above section describing intervertebral epidural catheter placement can be referred to for imaging techniques when viewing the spinal column.

Head & Neck Blocks: Head and neck blocks are often performed in infants and children for managing pain in the postoperative period. Although these blocks are simple and easy to use, the prevalence of their use has been lower than expected due to inexperience as well as the need for education of surgeons regarding their use. Two common blocks that we use in our practice are the infraorbital nerve blocks and the superficial cervical plexus block.

Infraorbital nerve blocks: The infraorbital nerve is the terminal branch of the trigeminal nerve (V1). This nerve, as it exits the maxillary foramen supplies the sensory innervation to the upper lips, the maxillary sinus area and parts of the nasal septum. We have used it successfully for infants undergoing cleft lip repair as well as in sinus surgery.[12]
Technique: The upper lip is everted, using a 27_G needle, it is advanced towards the infraorbital foramen, after careful aspiration 1 mL of 0.25% bupivacaine is injected. The area is gently massaged to allow easy spread of the local anesthetic solution.
Adverse effects: The upper lip remains numb after the block and some children may find it distressing. In addition, a small hematoma can develop at the site of injection.

Superficial cervical plexus block: The superficial cervical plexus is derived of the cervical nerve roots and supply the pain fibers for the neck, the pinna and the mastoid area. The superficial cervical plexus wraps around the belly of the sternocleidomastoid to supply the anterior neck as well as the mastoid area with its branches, the great auricular, the lesser occipital, the transverse cervical and the supraclavicular.
Technique: Using a sterile technique, the sternocleidomastoid is identified at the level of the cricoid cartilage(C6), a 27- g needle is inserted along the posterior border of the sternocleidomastoid, after careful aspiration, 2 mL of 0.25% bupivacaine is injected to provide pain relief. We have used this technique for children undergoing mastoid surgery repair as well as for cochlear implants.[13]
Adverse effects: Serious adverse effects can be seen from injection into a blood vessel but with superficial injection, there is little chance for major problems.

Suprazygomatic Maxillary Nerve Block: This block has been demonstrated to be very effective in the management of cleft palate repair in children[14]. The suprazygomatic approach from the frontozygomatic angle is one of the safest recommended approaches to the foramen rotundum, which limits needle insertion trajectory to avoid inadvertent puncture of the intraorbital contents through the infraorbital fissure.

The advent of US imaging has resulted in rapid development of different US guided approaches in recent years, including the suprazygomatic maxillary nerve block. Real-time ultrasound guidance minimizes the risks of nerve damage or vascular puncture, but allowing direct localization of the internal maxillary artery, needle positioning, and spread of LA solution. The US probe is placed over the maxilla and under the zygomatic bone, inclined at 45^{o} in the frontal and horizontal planes. Visualization is of the pterygopalatine fossa, with the maxilla at the anterior, and greater wing of the sphenoid posteriorly.

Following puncture at the frontozygomatic angle, located at the junction of the upper edge of the zygomatic arch and the frontal process, the needle is advanced perpendicular to the skin to reach the greater wing of sphenoid at approximately 20 mm of depth, then withdrawn several millimeters and redirected toward the nasolabial fold in a 20^{o} forward and 10^{o} downward direction, progressing in the direction of the pterygopalatine fossa.

To produce effective anesthesia in the maxillary area, the needle is introduced through the pterygomaxillary fissure to the fossa. The needle is advanced using an out-of-plane approach while visualizing the needle under US. Under US the pterygopalatine fossa is bounded by the root of the pterygoid plates, the inferior surface of the greater wing of the sphenoid bone, and the posterior surface of the maxillary bone. It appears on US as a funnel limited by these surrounding structures. The internal maxillary artery is readily visualized in most patients, with a two-dimensional pulsing. Advancement through the temporalis muscle is acknowledged with a loss of resistance and marks appropriate puncture depth. Following performance of a blood aspiration, US can be used to see the spread of local anesthetic in the pterygopalatine fossa and should be clearly observed in >90% of cases.

Upper Extremity Blocks
The most common approach to the brachial plexus in infants and children is the axillary approach and the supraclavicular approach. With the advent of US guidance, the interscalene approach has resurfaced as a viable technique for placement of a catheter. Peripheral catheter use is increasingly used, following good safety data.[15]

Interscalene Block
Sonoanatomy: A small footprint hockey stick probe will allow optimal recognition of the superficial structures in this region for infants and small children. In a transverse oblique plane at the level of the cricoid cartilage and at the posterolateral aspect of the sternocleidomastoid muscle, the superficially-located sternocleidomastoid muscle appears triangular in shape and overlies the internal jugular vein and common carotid artery. In small infants, the US probe footprint is wide enough to capture the great vessels along the brachial plexus in the same image screen. Lateral to the vessels and deep to the sternocleidomastoid muscle lies the anterior scalene muscle, and more posterolaterally, the middle and posterior scalene muscle (the latter two often appearing as a single mass). The hyperechoic (bright)-appearing tissue forming a lining around the muscles is presumably the fibrous tissue of the interscalene sheath. Brachial plexus trunks and/or roots in this sagittal oblique section are usually visualized as three (or more) round or oval-shaped hypoechoic (grey or dark) structures, lying between the scalenus anterior and medius muscles.[16] Continuous interscalene blockade was performed for a 10-year old girl in the Philippines during a plastic surgery medical mission with an intravenous catheter.[17] Without the availability of perineural catheters as well as stimulating needles, a 22 gauge angiocatheter was used for the block, utilizing an in-plane alignment to the posterior

edge of the probe using the US equipment from the obstetric suite. This case demonstrates the ubiquitous nature of US equipment in most medical centers across the globe.

Supraclavicular Block

Sonoanatomy: The probe is placed along the upper border of the clavicle. The carotid and the internal jugular vein are recognized. The probe is moved laterally while looking for the pulsation of the subclavian artery. The supraclavicular brachial plexus is located lateral to the artery and appears hyperechoic mixed with hypoechoic shadows in a grape like fashion surrounding the artery.

Technique: The supraclavicular block is performed using a high frequency hockey stick or linear probe. The subclavian artery to identified, inferior to it is the dome of the pleura and lateral and inferior to it is the 1st rib. The plexus can be accessed using an in-plane approach from laterally. Nerve stimulation can be used in conjunction with US guidance for this block.

Comment: When performing a supraclavicular block there is a greater risk of pneumothorax as the cupola of the lung lies just medial to the first rib, not far from the plexus; the distance of the plexus from the lung being especially short in children. It is critical to ensure that clear visibility of the needle shaft and tip is obtained by aligning the needle in-plane to the ultrasound probe at all times. Single injection techniques are generally sufficient; however multiple injections of local anesthetic can be performed if needed with the needle redirected to ensure sufficient

circumferential spread around the plexus. However, care should be taken to avoid intravascular injection of the surrounding vessels (including the transverse colli artery located cephalad to the plexus). Auscultation of the lungs should be performed before and after performance of the block as well as prior to discharge to detect clinical signs of pneumothorax. A simple method to recognize the viability of the radial median and ulnar nerve can be performed by a 'thumbs up sign' radial nerve; flexion of PIP (median nerve) and scissoring of the fingers (ulnar nerve) prior to performance of the block to recognize prior injury.[18]

Clinical Pearls - Supraclavicular block

- Place a linear probe superior to the clavicle scanning lateral to the great vessels
- Notice the 1st rib and the subclavian artery
- The supraclavicular plexus is seen surrounding the subclavian artery as a 'bunch of grapes'
- Using an in-plane approach, place the needle below the plexus, injection of 0.3mL/kg of local anesthesia will produce adequate analgesia.
- Stay away from using a medially positioned needle due to close proximity to the pleura.

Axillary Block

Sonoanatomy: With the probe placed perpendicular to the anterior axillary fold, a short-axis view of the neurovascular bundle can be obtained; the biceps brachii and coracobrachialis muscles are seen laterally; the triceps brachii muscle is medial and deep to the biceps brachii muscle. The anechoic and circular pulsating axillary artery lies centrally, adjacent to both the biceps brachii and coracobrachialis muscles, and is surrounded by the nerves. The *median* nerve is typically located superficial and between the artery and biceps brachii muscle, the *ulnar* nerve is commonly located medial and superficial to the artery, and the *radial* nerve often lies deep to the artery at the midline. At this level, the musculocutaneous nerve is located between the biceps brachii and coracobrachialis muscles.

Technique: The terminal nerves are visualized in an axial plane, the probe is placed in the axillary fold. A needle is placed in an in-plane approach to access the median, radial and ulnar nerves individually. Local anesthetic solution is placed to surround the plexus in its entirety to provide an adequate blockade. We feel that the use of ultrasound may allow reduction in dosing for the block although further studies are required to prove the pharmacodynamic ability of US guidance with lower volumes for axillary blocks in children.

Comment: Multiple injections and needle redirections are commonly required to ensure circumferential spread of the local anesthetic around each of the individual nerves. Since there is an abundance of vessels in this region, complete avoidance of vessel puncture can be a challenge even when utilizing ultrasound imaging. It is important to understand that the plexus remains very close to the surface and hence the needle should be directed cautiously while this block is attempted. Smaller doses can be used to provide an adequate blockade of this plexus in infants and children.

Axillary Block
- Place a hockey stick probe or a linear small footprint probe in the axilla as proximal as possible.
- The needle is directed from superior to inferior using an in-plane approach.
- The structures are superficial and hence are located fairly superficial and can be easily identified.
- Color Doppler can be used to recognize the vascular structures.
- Local anesthetic solution is injected to surround the cords.

Lower Extremity Block

Femoral Nerve Block:

Sonoanatomy: Similar to using conventional technique, arterial pulsations of the femoral artery is the key landmark when using US guidance for femoral nerve blockade. With the probe placed at the level of and parallel to the inguinal crease, the nerve appears lateral to the large, circular and anechoic femoral artery (color Doppler may be used to identify the femoral artery and vein). The nerve often appears triangular in shape and may be variable in size. The fascia

lata (most superficial) and iliaca (immediately adjacent to the nerve and in fact separating the nerve from the artery) are seen superficial to the femoral nerve and often appear as bright and longitudinally angled echogenic signals.[19]

Technique: A linear high frequency US probe is placed at the level of the inguinal crease and using an in-plane approach, the femoral nerve is accessed from the lateral aspect. Once the needle enters the fascia iliaca compartment, local anesthetic solution is injected to envelope the nerve entirely. If a nerve stimulator is used adjunctly, quadriceps contraction is elucidated. Although one cannot be sure about intraneural injection while using US guidance, it may be prudent to place the needle in the fascia iliaca compartment and not place it directly into the neural plexus.

Femoral Nerve Block
- Place a linear probe along the inguinal/femoral crease.
- Place a needle in an in-plane approach.
- The local anesthetic is injected to surround the nerve.
- The needle has to be placed inside the fascia iliaca compartment and the local anesthetic is seen surrounding the nerve bundle.

Lateral Femoral Cutaneous Block:

Sonoanatomy: The lateral femoral cutaneous nerve is located at the lateral aspect of the insertion of the Sartorius and medial to the tensor fascia lata. The nerve is located between the fascia lata and the fascia iliaca. This supplies the lateral aspect of the thigh and can be used for providing analgesia for surgery to the lateral aspect of the thigh including muscle biopsies[20] and for percutaneous hip pinning.

Technique: A finger is placed to identify the ridge between the tensor fascia lata and the Sartorius. A linear probe is placed straddling the tendinous ridge. The fascia between the tensor fascia lata and the Sartorius houses the lateral femoral cutaneous nerve. After sterile preparation, a 22-G needle is inserted through the fascia lata , after aspiration, 5 to 10mL of local anesthetic solution is injected.

Complications: Rare, bruise at the site of injection.

Sciatic Nerve Block:

Sonoanatomy: The sciatic nerve block is commonly used in children for providing analgesia for lower extremity surgery. We use it in combination with a femoral nerve block for providing analgesia for knee surgery. The sciatic nerve is usually scanned at the level of the popliteal crease. The biceps femoris tendon is identified. The popliteal artery is identified with the popliteal vein on top of the artery. Immediately above that is the tibial nerve. On scanning further laterally, the common peroneal nerve can be located.

Technique: In the supine or prone position, the popliteal fossa crease is identified, a linear US probe is placed at the level of the popliteal crease. The popliteal artery is identified, the popliteal vein deeper to it and deep to that structure is the tibial nerve. The US probe is moved laterally to visualize the common peroneal nerve. The probe is advanced cephalad to where the common peroneal and tibial nerves coalesce to form the single sciatic nerve. A

needle is placed in an in-plane orientation; the sciatic nerve can be stimulated if a stimulating needle is used to elicit inversion or eversion of the foot.

Sciatic Nerve Block at the Popliteal Fossa

- Place a linear probe in the popliteal fossa at the crease at the knee.
- Look for the popliteal artery.
- The popliteal vein is noted above the artery.
- The tibial nerve is often located in close proximity to the popliteal artery.
- The common peroneal nerve is located lateral to the tibial nerve.
- A linear probe is gently moved cephalad until the two branches confluence; the nerve will diverge from the vessels.
- Using an in-plane approach, a needle is placed in close proximity to the sciatic nerve and local anesthetic solution is injected to surround the nerve.

Blockade of the Anterior Trunk

Among many blocks performed at the anterior trunk, ilioinguinal/iliohypogastric nerve blockade is one of the most commonly performed blocks for surgery in the inguinal region and may be one of the most common peripheral nerve blocks in children.[15] Various other nerve blocks are also becoming popular to provide analgesia for procedures in the umbilical or epigastric regions. Ultrasonography can be particularly beneficial for truncal blocks in children due to the close anatomical relations between the nerves and various critical abdominal structures.

Ilioinguinal/Iliohypogastric Nerve Block

Sonoantomy: A linear high frequency probe is placed immediately medial to the superior aspect of the anterior superior iliac spine (ASIS) to capture a short-axis view of the ilioinguinal nerve sandwiched between the internal oblique abdominal and transverse abdominal muscles. The ASIS appears hypoechoic (due to dorsal shadowing beyond the highly-reflective periosteum) and nodular-shaped at the lateral edge of the screen. The lateral abdominal muscles will appear with multiple hyperechoic dots within a hypoechoic background. The nerve can be identified as an elliptical-oval shaped structure with a hyperechoic film surrounding a hypoechoic core.[21, 22]
Technique: A hockey stick probe will be suitable for many infants and younger children, since the nerves are closely situated beneath the skin (8 mm on average) and medial (7 mm on average) to the ASIS. The probe is placed with the direction pointed towards the umbilicus. A needle is inserted in an in-plane approach to place in between the internal oblique and the transversus abdominis muscle. Local anesthetic solution is injected to hydro-dissect between the two layers thereby providing a blockade of the L1 nerve root. We use a volume of 0.1mL/kg with a total maximum volume of 5mL for this blockade.

Ilioinguinal Nerve Block

- Place a linear probe or a hockey stick probe along the ASIS with the probe oriented towards the umbilicus.
- The three layers of the abdominal wall muscles can be recognized.
- The ilioinguinal nerve and iliohypogastric nerves are seen as 2 hypoechoic structures between the internal oblique and transversus abdominis muscles.
- Using an in-plane approach, a 27-Gauge needle is advanced and placed between the internal oblique abdominal and the transversus abdominis muscle.
- After aspiration, 0.1mL/kg of local anesthetic solution is injected.

Rectus Sheath Block

Sonoantomy: The rectus sheath is located between the rectus abdominis muscle and the posterior rectus sheath. A small footprint probe will be suitable for viewing unilateral anatomy. The anterior and posterior aspects of the rectus sheath and the enclosed rectus abdominis muscle are visualized. The sheath appears hyperechoic with multiple linear layers, lying on the anterior and posterior aspects of the rectus muscle.
Technique: A linear high frequency probe is placed on the abdominal wall lateral to the umbilicus. Using an in-plane approach and coming in from laterally, a needle is inserted posterior to the rectus abdominis muscle but anterior to the posterior rectus sheath. Superior displacement of the rectus abdominis muscle is seen with injection

of the local anesthetic solution. This block can be used for umbilical hernia repairs as well as most midline abdominal surgeries involving the T10 distribution

Rectus Sheath Block

- A linear high frequency probe or a hockey stick probe is placed at the level of the umbilicus.
- The rectus abdominis muscle is identified along with the anterior and posterior rectus sheaths.
- Using an in-plane technique, a 27-gauge needle is advanced until it penetrates the space between the rectus abdominis and the posterior rectus sheath.
- 0.1mL/kg of local anesthetic solution is injected into the potential space between the posterior rectus sheath and the rectus abdominis muscle.
- Hydro-dissection can be used to find the exact plane since the space is small and may need exact localization.

Transversus Abdominis Plane (TAP) Block

Sonoantomy: The layers of the abdominal wall can be easily distinguished using ultrasonography. The thoraco-lumbar nerve roots (T10 to L1) provide the sensory supply to the abdominal wall. The nerves run in a plane between the internal oblique and transversus abdominis muscle, hence referred to as the transversus abdominis plane or TAP. A linear probe placed along the lateral aspect of the abdomen can distinguish the various layers of the abdomen including from superficially, fascia/fat, external oblique, internal oblique and the transversus abdominis muscle. A blockade at this level can provide analgesia for anterior abdominal wall surgery. This may be especially useful in infants and children who may have underlying coagulopathy, spinal dysraphism or as a rescue block following a failed neuraxial blockade. The block has been demonstrated to be effective for abdominal surgery in the adult population[23] and safe in children[24].

Technique: A simple step by step approach to this block has been recently described.[25]A linear high frequency probe or a hockey stick probe is used for the procedure. Recognize the various layers of the abdomen. A needle is inserted in the in-plane technique to enter the plane between the transverses abdominis and the internal oblique. Local anesthetic solution (0.2mL/kg) is injected. The downward movement of the transverses abdominis signifies correct placement of the needle in the TAP plane.

Paravertebral Block

Sonoanatomy and Technique: Paravertebral technique has been described in children[26] and various approaches in adults[27]. After positioning the patient in the lateral position for single PVNB or full prone for bilateral PVNB, the desired thoracic level is identified using surface landmarks. Traditionally, T7 has been thought to be the lower

Transversus Abdominis Plane Block

- A high frequency linear probe or a hockey stick probe is placed lateral to the umbilicus.
- Sliding the probe laterally, the three muscle layers of the abdominal wall are recognized (external and internal oblique abdominal and transverse abdominal).
- In the mid-axillary line, using an in-plane approach, place a needle between the internal oblique and the transverse abdominal muscles.
- As local anesthetic is injected, the plane is seen to expand with posterior movement of the transversus abdominis muscle.

border of the scapula whereas C7 is the vertebral prominence. A linear ultrasound probe is placed in a transverse orientation over the midline of the spine and desired dermatome. Characteristic hyperechoic inverted v shapes with an acousting shadow beneath are used to identify the spinous process. The spinous process is identified and moving the probe laterally and with slightly oblique rotating, reveals the tip of the transverse process, in the same view as the parietal pleura. The internal intercostal membrane is identified as a hyperechoic structure connecting the edge of the internal intercostal muscle to the lower edge of the transverse process.

A needle is then introduced in-plane several centimeters from the lateral edge of the US probe and advanced at an angle from lateral to medial until the needle tip is through the internal intercostal membrane, between the parietal pleura and acoustic shadow of the transverse process. It is visualized at all times and correct position within the

paravertebral space is confirmed by downward depression of the pleura with minor injection of several milliliters of saline and followed by verifying negative aspiration for blood and/or CSF, or air.

Conclusion: US guidance for peripheral and central neuraxial blocks are becoming the mainstay of regional anesthesia in children. As equipment improves and becomes more cost-effective, the use of US guidance may become the norm rather than the exception. Multiple hands-on workshops offered by the ASA, ASRA and SPA may shed greater insight into some of the common techniques. The steep learning curve for US guidance can be offset by offering it as routine curriculum for training residents and fellows in anesthesia training programs. A block-rotation (as offered by the fellowship program at the Ann & Robert H Lurie Children's Hospital of Chicago) can improve and reinforce the use of regional anesthesia in infants, children and adults. Ongoing data is being collected prospectively by the Pediatric Regional Anesthesia Network (PRAN)[28], a consortium of Children's hospitals in North America as well as international efforts in Europe[29]. As more data is collected, we will be able to provide a more meaningful insight into adverse effects, dosing and pharmacodynamics of regional anesthesia in infants, children and adolescents.

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Figure-6 Ilioinguinal N Block

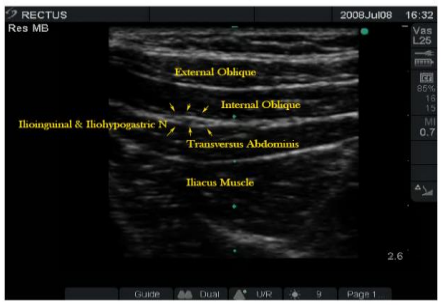
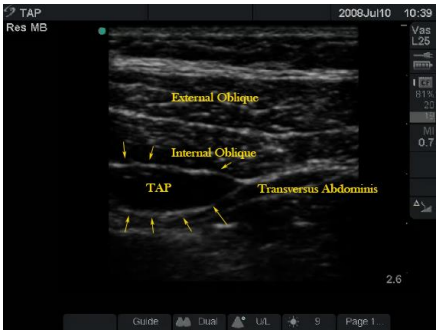


Figure-7 TAP block



ANESTHESIOLOGY 2017
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The Basics of the Business of Anesthesiology: Everything you need to know, but were afraid to ask

Andrew B. Leibowitz, MD **New York, New York**

Introduction

As Anesthesiologists we learned the science of medicine in medical school, mastered bedside skills and developed judgment during residency. Somewhere along the way through an ill-defined path we were supposed to figure out the business of anesthesia practice. The goal of this ASA refresher course is to equip every attendee with the knowledge they need to understand the business of healthcare as it specifically relates to their Anesthesiology practice.

I. Who pays us what?

Very few patients pay their bills entirely out of their own pocket.

The vast majority of patients have some form of insurance that often requires the patient to pay a part of their bill, usually a minority, based on their yearly deductible and agreed upon co-payments. Anesthesiologists are under pressure from their associated institutions and surgeons to be "in network," meaning that they have negotiated a set of contracted rates with the insurer and are considered "participating" (i.e., "par") physicians by the health plan.

The main insurers in the United States are:

1) **Medicare**, the federal insurance program created in 1965 (Title XIX of the Social Security Act), covers the elderly regardless of income, medical history, or health status, and persons with permanent disabilities (e.g., end stage renal disease). About 55 million persons are covered by this program, or about 15% of the population. Elderly recipients account for about 83% of Medicare expenditures and persons with permanent disabilities the other 17%. Notably, only about 11% of Medicare expenditures go toward physician payments.
2) **Medicaid** is a joint federal and state insurance program created in 1965 at the same time as Medicare, administered by the states to cover low income persons, qualified pregnant women and children, and individuals who receive Supplemental Security Income (SSI). About 74 million persons are covered by this program, or about 20 % of the population, 40% of all children, and 45% of all deliveries, making it the single largest source of health insurance coverage in the United States. The federal government covers about 2/3^{rds} of Medicaid expenses via transfer of monies to states, and state contributions cover the other 1/3rd. States administer their Medicaid programs very variably, with the money spent per enrollee ranging from as low as about $4000 per year in Nevada, to as high as $11,000 per year in Massachusetts, and a national average of $5700 per enrollee.
3) **Commercial insurers** cover most of the 65% of the population not covered by Medicare and Medicaid. These are large companies that may be for profit and often are publically owned (e.g., UnitedHealth Group – that covers about 70 million persons and has $180B/yr. in revenue, Aetna, Humana, Cigna), or ostensibly not for profit (e.g., some Blue Cross Blue Shield plans). Unlike Medicare and Medicaid, these commercial insurers pay hospitals and providers different fees for the exact same services based on negotiated rates. These companies frequently offer a myriad of insurance products ranging from plans they manage for Medicaid and Medicare, network negotiated services and rates, more restrictive Health Maintenance Organization type coverage, and mostly vanishing straight forward fee for service insurance.

Any large Anesthesiology group, or a group of any size providing service in a hospital, will need to participate in Medicare and Medicaid simply because they insure more than 1/3rd of the population and without participation, receiving payment is near impossible. Medicare and Medicaid typically pay for Anesthesia services (see section II)

at a rate much less than needed to generate a salary structure at even the 25%'ile (see section III). Therefore, a practice's mix of Medicare, Medicaid, "in network" commercial insurance, potential "out of network" collections, and hospital "subsidy" are the key elements that determine its potential financial solvency.

II. How is our work quantified?

The 1989 Omnibus Budget Reconciliation Act ended charges and reimbursements based on what were "usual, customary and reasonable." In place of this archaic and opaque practice a Medicare fee schedule was enacted based on the components of physician work (e.g., time, technical skill, mental effort and judgment), practice expense and malpractice costs. These components pertinent to Anesthesiologists boil down to work Relative Value Units, or what most physicians simply refer to as RVUs. The RVU scale is updated every 5 years by the American Medical Association, and the Conversion Factor (i.e., CF) is set by Medicare yearly. The ASA publishes its own RVU guide. The current average Medicare CF for an Anesthesiologist's RVU is approximately $22.00, but varies slightly by geographic area. The current Medicaid rate varies from state to state too, and is about 45-65% of the Medicare rate.

The total RVUs generated by a single anesthetic are the sum of a base unit assignment determined by the complexity of the case, 1 unit for every 15 minutes of Anesthesia time, and additional modifiers including ASA status, emergency nature of the case, etc. Various procedures including arterial line, central line, and echocardiography are assigned an RVU value too. Added together, the number of RVUs multiplied by the conversion factor determines the Medicare allowed payment, and Medicaid and commercial insurers employ a similar strategy. As noted in the preceding paragraph, in most areas of the country Medicaid pays significantly less than Medicare, and commercial insurers pay more, often pegged to some multiple of the Medicare CF. In addition, the Anesthesiology CF is different and is significantly lower (37% lower in 2016) than the CF for all other physicians.

Academic medical centers, large practices and corporate medical groups usually know the average or "blended" RVU reimbursement for all their physician groups, and their comparison to national averages. This generated RVU data can be used to quantify physician productivity and in many instances, help determine compensation targets. For anesthesiologists nationwide, the blended RVU value, equal to all of the RVUs generated divided by all of the payments received is estimated to be in the $35-40 range.

III. How much do Anesthesiologists earn? How can I find this out?

There are a variety of resources to determine Anesthesiologists' earnings.

For Anesthesiologists employed in Academic Medical Centers there are two main resources: 1) The annual American Association of Medical College's (AAMC) Faculty Compensation survey is usually initiated in August and results published in January (January 2016 issue titled "2014-2015 Report on Medical School Faculty Salaries"). These surveys are completed by medical schools with little to no departmental input. One hundred percent of the 144 United States Medical Schools participated in this most recent survey; 2) The Society of Academic Anesthesiology Associations (SAAA) also annually surveys all academic programs and about 66% of Departments participate. These surveys are completed by individual departments and the results are available to participating departments a few months after the survey deadline. This survey, like the AAMC survey, yields results for the previous year. The SAAA survey result is a privileged and confidential publication for use by the recipients only, it is not meant for distribution. Both surveys allow for breakdown of salaries into the 25th percentile, mean, median, 75th percentile and by academic rank. The differences between the surveys for all values are typically less 5%.

For Anesthesiologists not employed in Academic Medical Centers, there are many organizations including the Medical Group Management Association (MGMA), Delta and Merritt Hawkins & Associates, that collect and provide data similar to the AAMC and SAAA. Medscape conducts its own survey and in April 2016 did so with data for 2015 (http://www.medscape.com/features/slideshow/compensation/2016/anesthesiology#page=2). Anesthesiologists reported a mean compensation of $360,000 for the year (7th highest compensated physician specialty in the report). That report also broke down compensation by geographical area and revealed the highest mean compensation, $413,000, was in the "North Central" area (North Dakota, South Dakota, Nebraska, Kansas,

Iowa and Missouri) of the country, and the lowest, $342,000, in the Mid-Atlantic area (Pennsylvania, New Jersey, Delaware, Maryland, District of Columbia, W Virginia, Virginia, N Carolina and S Carolina).

Large publically traded Anesthesiology companies (e.g., MEDNAX Inc. (stock symbol MD), Team Health Holdings Inc., (stock symbol TMH)) and privately owned companies (e.g., North American Partners in Anesthesia, Sheridan) have less transparent compensation data.

IV. What is a clean bill?

A "clean bill" contains all of the elements accurately entered that the insurer requires, and the billing vendor compiles, in order to process it. For operating room anesthesia, at minimum this "clean bill" must contain patient's demographics including date of birth, address and telephone number, the patient's insurer's information, date(s) of service, the CPT code of the surgical procedure, the ICD 10 code of the diagnosis, the anesthesia CPT code and anesthetic duration. The bill or record stream must be properly signed and attested to. Attestation is especially important when supervising care provided by a CRNA or resident.

Coding for critical care and pain procedures may be more complex. Critical care billing entails its own evaluation-and management CPT coding, in addition to ICD10 coding; it requires a thorough knowledge of what must be contained within the progress and procedure notes. Pain care billing may require subspecialty referrals and pre-authorizations and is subject to very frequent changes in requirements that vary from payer to payer.

Most importantly, failure to institute a procedure that guarantees basic information flowing from the practice to the billing company is a recipe for disaster. Generation of a clean bill should be the least of any successful practice's concerns.

V. What is charge lag and how does it impact funds flow?

Charge lag is the time elapsed between closing a patient encounter and the submission of a claim to the insurer. Ideally, charge lag would approach zero, as it does for all usual cash and credit card purchases, but dependency on insurers to pay first, and then the patient to cover the deductibles, co-pays, etc., translates into a variable period of time to collect all charges due, dependent on a practice's billing and collection efficiency (boutique, cash only practices do not face this obstacle). Charge lag for OR anesthesiology claims is probably in the 5-10 day range in most practices, and for critical care and pain claims, longer, but this is very variable and dependent on the electronic record keeping system, physician meticulousness, communication utilizing IT dependent resources with the biller, and the biller's turnaround time from receipt of all required information to claim submission.

Any increase in charge lag will result in slower cash flow into the practice. Very long delays may in certain cases jeopardize the insurer's payment entirely, and the further an episode of care is from the receipt of a bill by the patient for the deductible and copay, the less likely it is to be collected in a timely fashion, if at all.

VI. What is accounts receivable and gross collection rate?

Accounts receivable (A/R) is the sum of outstanding charges owed to a practice. Because there is a lag between provision of service and receipt of payment, all practices have A/R and the tracking and management of A/R is a basic business function. "Days in AR" is calculated by dividing the accounts receivable by the average daily charges. For example, "45 days in A/R" means that the practice is due payment for the equivalent of 45 days of work. Given that in Anesthesiology a typical bill is paid in 50-70 days, the days in AR should be in the 50-70 day range. Fewer days in AR is a sign of a very efficient billing practice (sometimes referred to as revenue cycle), but could also represent a practice that quickly writes off uncollected charges, whereas closer to 70 or more days denotes inefficiency, and cash flow that is less than ideal. Alternatively, more days in AR will always accompany practices with a large volume of out of network patients and patients with large deductibles and co-pays. A/R is often separated into "buckets," usually <-60, 60-90, 90-120 and > 120 – so that all money owed is tracked as to how long it has been owed for, and the performance of the practice over time can be trended using historical performance. The majority of A/R (i.e., >50%) for OR Anesthesiology care should reside in the < 60 days bucket.

Gross Collection Rate (GCR) is another basic business metric. Charges always exceed collections. Almost all practices create a charge that they hope their very best customer might pay, usually exceeding contracted rates (because contract clauses often state "lesser of this fee of billed charges…" it is not in a practice's interest to ever have a fee schedule where this might come into play), knowing that most commercial insurers will pay less, and Medicare and Medicaid will pay much less. Therefore, the calculated GCR may be as low as only 25-35%. Because of this, it is also useful to know the net GCR that reflects the genuine expected charge that the payers will consider; this "net" GCR should be in the > 90% range. Gross charges are one way, in addition to RVUs billed, for practices to track their work effort. Ideally gross charges and RVUs should track each other in parallel and can be used interchangeably for the purpose of estimating total work effort.

VII. What are the costs of running a practice?

Obvious costs include collection services (usually 3-6% of collections), malpractice insurance (e.g., $12-18K / MD) and benefits. Benefits provided in whole or part by an employer including, organized from most to least expensive: 1) health, dental, vision insurance coverage; 2) contributions to the employee's 403(b) - in the case of a non- profit and 401(k) - in the case of a for profit defined retirement contribution plans; 3) life and disability insurance; 4) other - including license, DEA, society memberships, CME sponsoring.

Employers also incur FICA (Federal Insurance Contributions Act) taxes, sometimes referred to as "payroll" taxes. These include Medicare (1.45% on the entire salary) and Social Security (6.2% on salary below the "wage base limit" currently ~$127,000).

Less apparent to many employees are the costs of running a practice. These include employing persons involved in answering the phone, submitting critical documents including privileging and credentialing packets to hospitals and insurance companies, responding to patient complaints, dealing with issues of discipline, regulatory compliance - FPPE and OPPEs, IT support and the frequent legal issues accompanying all contracts with insurance companies, hospitals, ASCs, employees and hired, and sometimes fired, Anesthesiologists.

Pain practices are dependent on highly educated staff to obtain pre-authorizations, and might also require highly trained radiology technicians and medical assistants in order to perform procedures safely and efficiently. Depending on where Pain procedures are performed and contractual agreements with the sites or hospitals, these assets are often paid for by the facility.

VIII. Alternative payment models and bundles

Increasingly insurers, especially Medicare, are looking to move away from the fee for service payment model toward using payments to encourage and promote a combination of excellence in care, and shared responsibility for minimization of cost. The equation: value = quality ÷ cost, is inescapable in daily life and the "triple aim" of improving the patient experience, improving the health of the total population and reducing the per capita cost of health care is an inescapable government mantra.

There are numerous acronyms accompanying these efforts and include MACRA, MIPS, APM, NACOR, QCDR, PQRS, AQI to name just a few. The bottom line is that Anesthesiology practices in combination with their primary care counterparts in some instances, or as stand-alone entities, will need ways to demonstrate the quality of their care to insurers who pay them, and will pay them less, or more, depending on the perceived quality of their care based upon the "proof". Reporting the measures proving quality will almost always require an electronic medical record, a means of extracting the pertinent information to calculate the numerator and denominator, transmitting that data to a qualified clinical data registry (QCDR), and that registry transmitting the data to the insurer. The Merit Based Incentive Payment model that I currently participate in is anticipating the reporting of 7 measurements in order to avoid a 4% reduction in Medicare reimbursements, and possibly achieve a 4% increase instead, for a an increasing difference in the future of as much as 18% in 2022, or approximately $3.95 per RVU. Anesthesiology

practices that are part of Accountable Care Organizations (ACOs) may be able to latch onto the ACO's reporting and avoid performing their own data collection and reporting.

Bundles are Medicine's equivalent of an all-inclusive resort hotel. Bundles are an attempt by Medicare and some commercial insurers to issue one lump sum payment for all services incurred for certain diagnoses and procedures including hospital, physician and post discharge services. Bundles are now being rolled out for the most reproducible of procedures including hip and knee replacements, isolated coronary artery bypass grafting, and certain transplants. To date, very few physicians have veered from simply receiving fee for service payments while participating in bundled payments because so far they have been arrangements between health systems and hospitals who incur the risk of getting paid less by the insurer if their costs do not meet the target. Success in any of these schemes is predicated on controlling costs that become astronomical during prolonged length of stays, and unplanned care including readmissions; so minimizing variations in care, eliminating costly complications (e.g., infection, deep vein thrombosis), and providing home services aimed at reducing readmissions often become the focus of the hospitals and physicians who participate in bundled payments.

It is anticipated that in the near future, physicians and hospitals will negotiate with payers for a total bundled payment, and then with each other for their share of the payment. The negotiations between hospital and physicians will be very complex, and likely adversarial. Consideration of how a patient comes to a certain practice, the role of each individual physician, how the costs of an outlier or readmission are attributed – perhaps with an a priori established "stop loss fund," etc. will all factor in to these negotiations. Insurers may base their intended total reimbursements on a local "reference case," that is a center performing the service with an average or above average quality outcome, and an average or below average total cost. This may lead to a bidding war in a race to the bottom in markets where there are several entities providing the same service if they each have less than ideal utilization and decide to implement a "get paid less per case, do many more cases" approach. The California Public Employee's Retirement System (CalPERS), covering more than 2 million persons, has already instituted such a reimbursement scheme and has driven competing hospitals and systems to a single price point.

IX. What is the financial implication of MD-alone v MD-CRNA anesthesia care?

This is a very complex question and depends upon whether you practice in opt in or opt out state. There is a federal requirement that CRNAs must be supervised by a physician, but states may "opt out" of this requirement, and thus far 17 states have. For purposes of this review, consideration will be limited to those states that require anesthesiologist supervision.

The financial determinants are: 1) the ratio of coverage (e.g., 1:1, 1:2, 1:3, or 1:4); 2) the length of the workday (e.g., 8:00 AM- 3:00 PM v 7:30 AM- 6:00 PM; 3) CRNA shift duration (e.g., 8, 12, 16 hours); and 3) the terms of employment including total compensation, benefits, and time off. In general Anesthesiologists, especially those with an ownership or profit motive, have more flexible work hour expectations, do not expect to leave at very specific times, and work a greater number of hours per week than a CRNA. Anesthesiologist's adaptability in this regard when working in areas with difficult to anticipate end times, and unexpected emergencies or delay in PACU discharges is difficult to quantify, but in practical terms is priceless.

A common example is using a possible 1:3 coverage model to cover increments of 3 rooms. If a small practice is staffed with only MD's who are willing to work 10 hours a day (e.g., 7:30 AM – 5:30 PM), and all rooms always finish within or near that time frame (a 50 hour work week), 15 MD shifts per week are required and if every physician has 5.2 weeks off per year then exactly 3.3 MDs will be required. Supervision of CRNAs doing four 10 hour shifts a week that also have the same 5.2 weeks off per year would require 1.1 MDs and 4.1 CRNAs. From a purely financial perspective, the costs will be disadvantageous when 4.1 CRNAs are compensated more than 2.2 MDs, and using Medscape and other surveys noted above in section III as guidance, this is the case thru-out the majority of the U.S.A. For most scenarios, 1:4 coverage will almost always be financially advantageous and 1:2 coverage will almost always be financially disadvantageous relative to an MD alone model.

X. I want to buy a money generating piece of equipment, when will it pay for itself? How can I sell the idea to my administrator?

This question usually arises in the non-operating room areas, especially in Pain practices and in Intensive Care Units. Examples include: 1) A Pain practice wants to purchase equipment to create platelet rich plasma for which they charge new fees to inject; or 2) the Intensivists want to purchase new fluoroscopy and ultrasound machines and go into the practice of placing peripherally inserted central venous catheters (PICCs) for hospitalized patients who perhaps would then be discharged home earlier. This gives them something to do during their non-ICU time, makes good use of their access skills, and will generate revenue, so it all sounds plausible.

Setting aside the main question of whether or not the procedure is appropriate for patients, the point of this review is to dissect the underlying business aspects of the purchases that include; 1) the purchase price of the device and required associated equipment (e.g., lead gowns); 2) the life expectancy of the device in uses or years; 3) the per use costs (e.g., PICC line insertions will require a sterile ultrasound probe cover, gown, gloves, masks, line kit, dressings, etc.) that might be covered by a separate technical fee; and 4) the physician reimbursement per procedure.

A basic formula is:

Breakeven Point i.e., (# of procedures) = Purchase cost ÷ (Ave. Reimbursement per procedure – Cost per Procedure)

In very basic terms if we will assume that the cost of the procedures are part of the practice's fixed costs, meaning that the practice will not pay extra for the space, electricity, or the equipment to do each and every individual procedure, then there is no cost per procedure , and in this case then :

Fluoroscopy machine cost $30,000
Dedicated new ultrasound machine costs $10,000
PICC line professional fee is $90

Breakeven Point = (30,000 + 10,000) ÷ (90-0) = 444 procedure need to be performed to begin to turn a profit.

If this new service can place 2000 PICC lines a year it appears in 3 months' time it could generate a revenue stream of $180,000 per year (2000×90). But a physician can't do this alone – assistance with the patient positioning, readiness, and a fluoroscopy machine etc will also be necessary to run a safe and successful service. This could be accomplished with 1.1 FTE medical assistant paid $50,000 including fringe benefits to do 2000 procedures - then our financial view will be:

Breakeven point = (30,000+10,000) ÷ (90- (50,000/2000) = 615 lines need to be placed to break even. After 615 lines are placed this service will generate $130,000 per year [(2000 × 90) -50000].

The medical assistant is a fixed cost, so "profits" will be proportional to the number of procedures performed. This may not be the case when direct costs, those attributable to each and procedure comes into play. If for instance the practice had to pay the cost of the ultrasound probe cover ($3.00), then the equation for net revenue would be:

Net revenue per year = [($90 - $3 per procedure) × # of procedures per year] – $50,000 (yearly assistant's cost)

How can we justify all this work for such little return? Is there downstream economic benefit? The argument may be made that for every 10 patients that have a PICC, 1 patient goes home 1 day earlier because they can get their antibiotics at home now thru their PICC; the hospital will free up 200 patient days and a patient day is worth $800, thus saving the hospital $160,000! With this information we can approach the hospital to pay for the medical assistant and the one time acquisition of the fluoroscopy and ultrasound machine too. Perhaps, they will even help support part of the faculty member's salary for directing this service if we are very convincing.

XI. Managing the operating room and ancillary services

In order to be a business success – pay for all your employee's benefits and wages competitive with the local market place - and recruit and retain your workforce - requires that work be performed with an ideal number of persons to do the job. If the practice employs too few Anesthesiologists, the employer, ASC, Hospital or office, will go looking for another group; if the practice employs too many Anesthesiologists, incomes will be lower than desired and members will seek employment in another group.

One can focus on the simple output of all the employees and aim for a goal of RVUs per person $\geq$ average, but call responsibilities, pre-call and post call time off, etc. sometimes make this more difficult to implement than it might appear. However, this approach is used by many other specialties.

Tracking operating room efficiency is useful too. The main metrics to track are 1) on time starts (ideally > 75%); OR utilization rate (total anesthesia time per location ÷ total time an OR is available) that should also be > 75% but varies tremendously by type of case. A liver transplant that takes 10 hours to do will result in a 100% utilization rate, but 3 total joints done in the same 10 hours with a 40 minute room turnover time between cases will result in an 80% utilization rate and; 3) Case cancellation rate (should be as close to zero as possible). Failure to meet any one of these metrics equates to Anesthesiologists in the workplace not performing work, not generating revenue.

In a Pain practice similar metrics include: 1) RVU's per MD. Slower Pain doctors vs faster Pain doctors will have a major impact on the bottom line; 2) patients seen and procedures per "session"; 3) scheduling efficiency including cancellations, no shows and bump rate; 4) payer mix per MD 5) and maybe most important, patient satisfaction. Overall, successful Pain specialists will see more patients, do more procedures and generate a referral base of commercially insured patients.

Finally, in Critical Care, there is very robust RVU per provider data, usually averaging closer to 7500-8000 per year (less than the typical operating room anesthesiologist), and unless a practice has an unusual call burden, RVUs per MD is an easy means of tracking productivity and determining if more or fewer Intensivists are needed. Unlike Pain MDs, Intensivists have no control over their patient flow and no control over their payer mix, so those metrics have no applicable counterpart.

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ANESTHESIOLOGY 2017
BOSTON OCTOBER 21-25

Upper Extremity Regional Anesthesia: Essentials for Your Practice

Joseph M. Neal, MD **Seattle, Washington**

Dr. Neal has no conflicts of interest related to this presentation and receives no financial support from any entity other than his employer

Learning Objectives:
Upon completion, participants will be able to:
1. Distinguish those techniques that can improve block success
2. Recognize the nuances of local anesthetics and additives used for upper extremity blocks
3. Identify the prevention and treatment of block-related complications

Regional anesthesia for shoulder and arm/hand ambulatory surgery improves early outcome measures such as better analgesia, decreased opioid-related side effects, earlier readiness for discharge, and reduced frequency of unplanned hospital admission. After single injection blocks, these advantages do not exceed 24 hours and initial analgesia may be accompanied by significant rebound pain upon block resolution. Continuous perineural catheters consistently improve analgesia, and may facilitate earlier hospital discharge and rehabilitation after major shoulder surgery. This information is important, because it provides objective data that brachial plexus regional anesthesia can positively affect outcome in patients undergoing upper extremity surgery.

This refresher course lecture focuses on the selection of approaches to the brachial plexus, techniques to improve block quality, important pharmacologic considerations, and complications associated with upper extremity neural blockade. Because of time and space constraints, actual techniques of performing upper extremity blocks will not be discussed. Participants are referred to classic textbooks and atlases for this information.

APPROACHES TO THE BRACHIAL PLEXUS

Knowledge of surgical site and brachial plexus anatomy combine to determine one's approach to the brachial plexus. The interscalene approach is ideally suited for shoulder surgery, but less appropriate for surgery distal to the elbow because of its propensity to spare the lower trunk (ulnar distribution). The supraclavicular approach is appropriate for most upper extremity surgery, although shoulder surgery may require supplemental supraclavicular nerve (C3-C4) block. The infraclavicular approach provides anesthesia distal to the shoulder and is consistently superior to the axillary approach for hand and arm surgery, in part because it more efficiently anesthetizes the axillary and musculocutaneous nerves. The axillary approach provides anesthesia for surgeries of and distal to the elbow, but specific blockade of the musculocutaneous nerve is advised if the surgical field involves the volar radial forearm.

TECHNIQUES THAT IMPROVE BLOCK SUCCESS

Nerve Localization

Despite over a century experience with brachial plexus blockade, studies have failed to identify a superior method to localize nerves. Indeed, block success (a term that unfortunately encompasses multiple definitions) plateaus at 90-98% regardless of whether nerves are localized using peripheral nerve stimulation, paresthesia, or in the case of axillary block, perivascular techniques. When compared to peripheral nerve stimulation, randomized clinical trials variably show that the use of ultrasound-guided regional anesthesia (UGRA) improves block onset, reduces block performance time and the number of needle passes, and results in more reliable blockade of the lower trunk via the interscalene approach. However, rates for surgical readiness and block success are similar. With the exception of reduced local anesthetic systemic toxicity (LAST), studies of UGRA have yet to prove increased safety as compared with other localization techniques.

Ideal Number of Injections
Regardless of how a nerve is located, the ideal number of injections to optimize block quality is block- and localization technique-specific. Ultrasound-guided blocks are typically multiple injection techniques that surround the nerves with local anesthetic. Nerve stimulator-guided interscalene and supraclavicular approaches to the brachial plexus achieve reliable blockade after a single injection. As the brachial plexus architecture begins to diverge into more widely spaced components, the value of increasing the number of local anesthetic injections becomes evident. Double or triple ultrasound-guided injection leads to faster supraclavicular block onset. Infraclavicular brachial plexus block is improved with double rather than single injection, particularly when one of the stimulations involves the posterior cord. A single posterior injection appears adequate for UGRA techniques. Landmark-based axillary blocks are improved by using three, but not four, injections. Injecting near the radial nerve is most important for attaining optimal anesthesia using the axillary approach, while injecting near the ulnar nerve is least important. Recent studies suggest that a two-injection ultrasound-guided technique (injecting at the musculocutaneous nerve and at the 6 o'clock position below the axillary artery) may be equally efficacious to a triple- or quadruple-injection nerve stimulation technique.

Continuous Perineural Catheters
Extended analgesia can be accomplished with continuous perineural catheters. Particularly for painful shoulder surgeries, continuous perineural catheters provide superior analgesia, limit opioid-related side effects, and improve patient satisfaction and sleep. This technology has proven useful and safe for outpatients. There is less evidence that perineural catheters improve economically-sensitive parameters such as earlier return to work, long-term rehabilitation, or other health-related quality of life measures.

PHARMACOLOGIC CONSIDERATIONS

Local Anesthetics
Local anesthetic selection for upper extremity regional anesthesia is determined primarily by the desired anesthetic and analgesic duration. There is no inherent advantage of one local anesthetic over another with regard to block quality, although limited data suggest that ropivacaine infusion preserves motor function better than bupivacaine. For single-injection brachial plexus blockade, bupivacaine 0.5% is equipotent to ropivacaine 0.75%, which implies that the advantage of reduced cardiotoxicity with ropivacaine may be offset if an increased mass (concentration x volume) of ropivacaine is required to overcome its reduced potency. There is no advantage to mixing a long-acting and an intermediate-acting local anesthetic—block onset is similar, but duration is shorter than would be achieved with the long-acting local anesthetic alone.

While it is intuitive to increase local anesthetic mass to optimize block characteristics, existing evidence suggests that doing so does not provide clinically relevant improvements when using traditional volume techniques, i.e., 20 mL or greater. Indeed, increasing local anesthetic concentration, volume, or total dose does not hasten block onset, improve quality, or prolong analgesia. Instead, increased concentration correlates with neurotoxic injury, while increased mass worsens LAST. Thus, modifying local anesthetic characteristics to facilitate neural blockade is ineffective, but conceivably places the patient at increased risk should nerve injury or LAST occur. Ultrasound-guidance further supports this concept, as excellent block characteristics are attainable using lower volumes of local anesthetic. However, there is emerging evidence that block duration may be reduced when extremely low volumes (less than 10 mL) are used. In the setting of continuous perineural analgesic techniques, evidence suggests that initial bolus dosing can be accomplished with relatively low volumes and concentrations of local anesthetic, e.g., 20 mL of 0.375% ropivacaine for interscalene block, followed by 0.1-0.2% ropivacaine infusion.

Additives
In the absence of continuous perineural techniques, limited prolongation of analgesia is achievable with local anesthetic additives. Yet despite a myriad of choices, only epinephrine, clonidine, and buprenorphene reliably prolong blockade from intermediate-acting local anesthetics. Those adjuvants do not significantly affect long-acting local anesthetics, whereas **dexmedetomidine** 150 mcg has been shown to increase the duration of ropivacaine interscalene blockade by about 4 hours. Dexmedetomidine as a perineural additive is an off-label use in the United States and has received limited human study; in one study its perineural effect was similar to that associated with intravenous administration. Perineural dexmedetomidine extends analgesia (by about 20%) as compared to clonidine

for supraclavicular block, but does so at the expense of sedation and transient bradycardia. **Epinephrine** prolongs peripheral nerve blockade by reducing clearance of the local anesthetic, in addition to serving as a marker of intravascular injection. Epinephrine 2.5 mcg/mL (1:400,000) achieves nearly the same block prolongation as 5 mcg/mL (1:200,000), but with less tachycardia and less reduction in peripheral nerve blood flow. **Clonidine** 0.5 mcg/kg prolongs anesthesia and analgesia by 50% for intermediate-acting local anesthetics, but <20% for long-acting agents (~2 hr. prolongation for either epinephrine or clonidine). However, clonidine can cause sedation (NNH 5) or hypotension (NNH 10) and lacks epinephrine's ability to signal intravascular injection. Clonidine is significantly more expensive than epinephrine; it is unclear if one is superior to the other or if indeed their actions are synergistic. Neither epinephrine nor clonidine improves sensory block quality when used during continuous infusion. **Buprenorphene** 0.3 mg prolongs duration of analgesia after axillary block. **Dexamethasone** has been shown in limited studies with widely disparate results to prolong the duration of mepivacaine analgesia to a degree similar to epinephrine or clonidine (~50%). However, recent commentary raises concerns about neurotoxicity with dexamethasone, particularly in diabetic patients or in doses that exceed 1 mg. Furthermore, dexamethasone studies that incorporate a systemic injection control group generally find little advantage of perineural injection as compared to intravenous injection. Recent meta-analyses conclude that if perineural dexamethasone results in greater block prolongation as compared to systemic administrative, the effect is limited (<4 hrs). Other additives—opioids, neostigmine, hyaluronidase, tramadol, and calcium channel blockers—serve no useful purpose in brachial plexus blockade, are reported without comparison to a systemic control group, or are incompletely studied with regard to neurotoxicity. **Alkalinization** of intermediate-acting local anesthetics does not accelerate brachial plexus block onset, despite its usefulness in hastening the onset of epidural block. Moreover, alkalinization has been shown in animals to actually reduce block duration and intensity. The use of **liposomal bupivacaine** around a neural plexus remains off-label and the dearth of published data limit any recommendation at this time. When compared to bupivacaine alone, the effect on worst pain during the first postoperative week of additional interscalene liposomal bupivacaine was modest (<2 numeric rating scale points).

COMPLICATIONS OF BRACHIAL PLEXUS BLOCKS

Local Anesthetic Systemic Toxicity

Two unique circumstances related to brachial plexus blockade affect LAST. First, seizures associated with local anesthetic injection are five times more likely to occur with peripheral nerve block than with epidural block. Second, brachial plexus approaches are particularly prone to systemic toxicity because they are often placed near arteries that directly supply the brain, thus seizures can occur after remarkably small doses of local anesthetic, e.g., 2.5 mg bupivacaine injected into the vertebral artery during the interscalene approach. Case reports document episodes of LAST despite the use of UGRA, although recent studies report ~65% decrease in the incidence of LAST when ultrasound-guidance is used rather than peripheral nerve stimulation. In accordance with the ASRA Practice Advisory on Local Anesthetic Systemic Toxicity, lipid emulsion should be readily available to treat local anesthetic toxicity wherever upper extremity blocks are performed.

Pneumothorax

Pneumothorax can occur with the supraclavicular approach; less so with the interscalene and infraclavicular approaches. Importantly, symptoms may not become noticeable for 8-12 hours following the block, particularly in the absence of positive pressure ventilation. Pleuritic chest pain is the most common presenting symptom, not dyspnea. Development of techniques designed in part to avoid the pleura, such as the plumb bob or subclavian perivascular approaches, or UGRA, have likely reduced the incidence of pneumothorax significantly, although no large studies confirm this impression. Based on reported cases, the risk of pneumothorax associated with ultrasound-guided supraclavicular block is 1:1000 (calculated upper limit, 95% confidence interval).

Vascular and Muscle Injury

Minor bruising occurs in up to a quarter of patients after axillary block. Serious vascular conditions—compressing hematoma, vasospasm, or arterial dissection—are rare, but should be considered in patients with postoperative neurologic impairment. The ASRA Consensus Conference on Anticoagulation and Regional Anesthesia suggests that deep brachial plexus blocks, e.g., supraclavicular or infraclavicular, not be undertaken in anticoagulated patients. Temporary myotoxicity can happen when local anesthetic, particularly bupivacaine, is infused into muscle.

Unintended Destinations of Local Anesthetics

Needles can be placed unintentionally near the neuraxis during interscalene block by advancing too far medial into the epidural, subdural, or subarachnoid space. The distance from the skin overlying the interscalene groove-to-the neuraxis is 23-35mm. Local anesthetic can also enter the subarachnoid space if a needle (seemingly placed at the proper depth) punctures a particularly long dural root sleeve. (Figure 1) When local anesthetic reaches the neuraxis, high spinal anesthesia or massive epidural anesthesia develops, which may be particularly difficult to diagnose in an anesthetized patient. If this happens, patients may present with unexpectedly high, and bilateral, sensory and motor block, bradycardia, hypotension, or asystole. Treatment is the same as for hypotension / bradycardia following spinal anesthesia, and includes early epinephrine to increase heart rate, contractility, and coronary perfusion pressure.

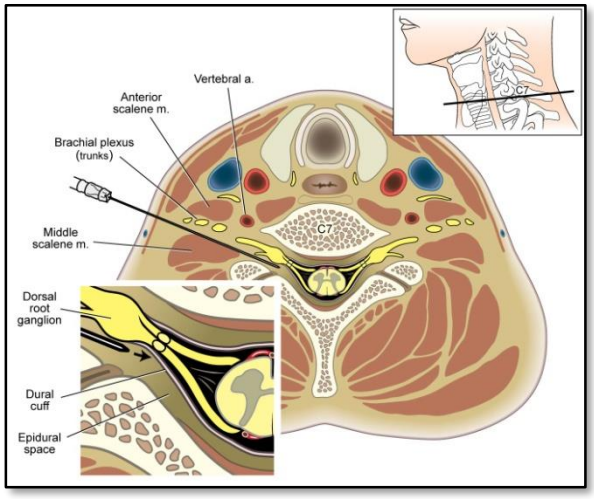

Figure 1. Neal & Rathmell, 2013

Unintended destinations of local anesthetics can also result in nuisance symptoms such as Horner's syndrome from blockade of the cervicothoracic sympathetic trunk, or hoarseness from blockade of the vagus and/or recurrent laryngeal nerves. These symptoms dissipate with resolution of local anesthetic blockade.

Hypotension / Bradycardia

Awake or mildly/moderately sedated patients who undergo interscalene brachial plexus block and are placed in the beach-chair position are reported to develop sudden hypotension and bradycardia in 13-24% of cases. These hemodynamic changes typically occur about an hour after block placement. The etiology of this condition is unclear, but is believed to involve relative preload deficit (from the sitting position) plus increased ventricular contractility (from exogenous and endogenous epinephrine), both combining to (arguably) activate the Bezold-Jarisch reflex. (Figure 2) Incidence can be reduced with metoprolol pre-treatment, but not glycopyrrolate.

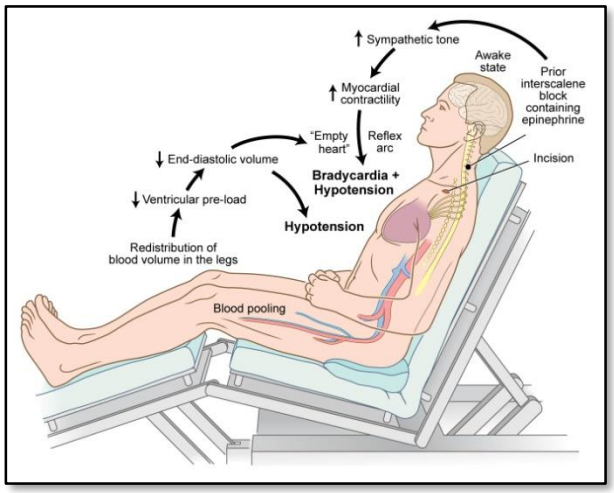

Figure 2. Neal & Rathmell, 2013

Inadequate Cerebral Perfusion

Rare cases of cerebrovascular accident have been reported in patients undergoing shoulder surgery in the beach chair or upright position. Although not specifically a complication of upper extremity regional anesthesia, practitioners should be aware of this complication, the etiology of which is not entirely certain, especially its association with hypotension. Nevertheless, issues of particular concern include measuring blood pressure at the appropriate site or performing hydrostatic calculations to accurately reflect pressure at the level of the brain (1.33cm from cuff to brain = 1mmHg reduced pressure at the brain). (Figure 3) Some experts argue that patients in the beach chair position should maintain mean arterial pressures of at least 75 mmHg (measured at the arm).

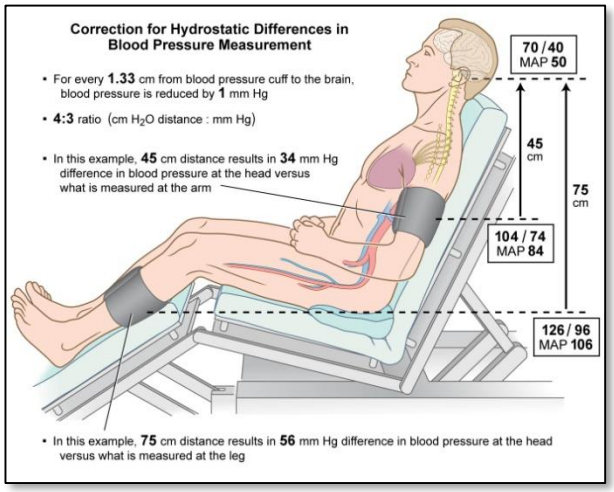

Figure 3. Neal & Rathmell, 2013

Complications of Continuous Perineural Blocks

Continuous perineural catheters do not appear to consistently increase complication rates as compared to single-injection techniques. Within the limitations of relatively few published studies, nerve injury does not appear to be increased. Similar to single-injection interscalene block, nerve injury has been associated with catheter placement in anesthetized patients. While the incidence of bacterial colonization is high (~39%), actual abscess formation is low (0.07%).

Hemidiaphragmatic Paresis

All landmark-based interscalene blocks and ~50% of supraclavicular blocks result in temporary hemidiaphragmatic paresis (HDP) secondary to anesthesia of the phrenic nerve. During interscalene anesthesia, a small subset of patients experience 25-32% reduction in pulmonary spirometric values. Pulmonary function is unaffected in healthy volunteers whose hemidiaphragm is paretic following supraclavicular block, but this may not be the case in patients with compromised pulmonary function. The incidence and severity of HDP can be reduced, but not completely and predictably eliminated, when local anesthetic volumes are decreased to 5-10 mL using UGRA. The ultrasound-guided approach probably blocks the phrenic nerve because of its proximity to the C5 nerve root. (Figure 4) Above the clavicle blocks are relatively contraindicated in patients unable to withstand a ~30% reduction in pulmonary function. Hemidiaphragmatic paresis following infraclavicular block is rare with the coracoid approach, but ~25% of patients who undergo the (more medial) vertical infraclavicular approach develop HDP with an accompanying 30% reduction in spirometric values.

Recently investigators have described novel techniques to reduce the incidence of HDP or grip strength diminution without sacrificing analgesia after major shoulder surgery. Such approaches include using the anterior approach to suprascapular nerve block for either single injection or continuous techniques. Less well studied is the combination of suprascapular nerve block with the infraclavicular approach to reduce HDP.

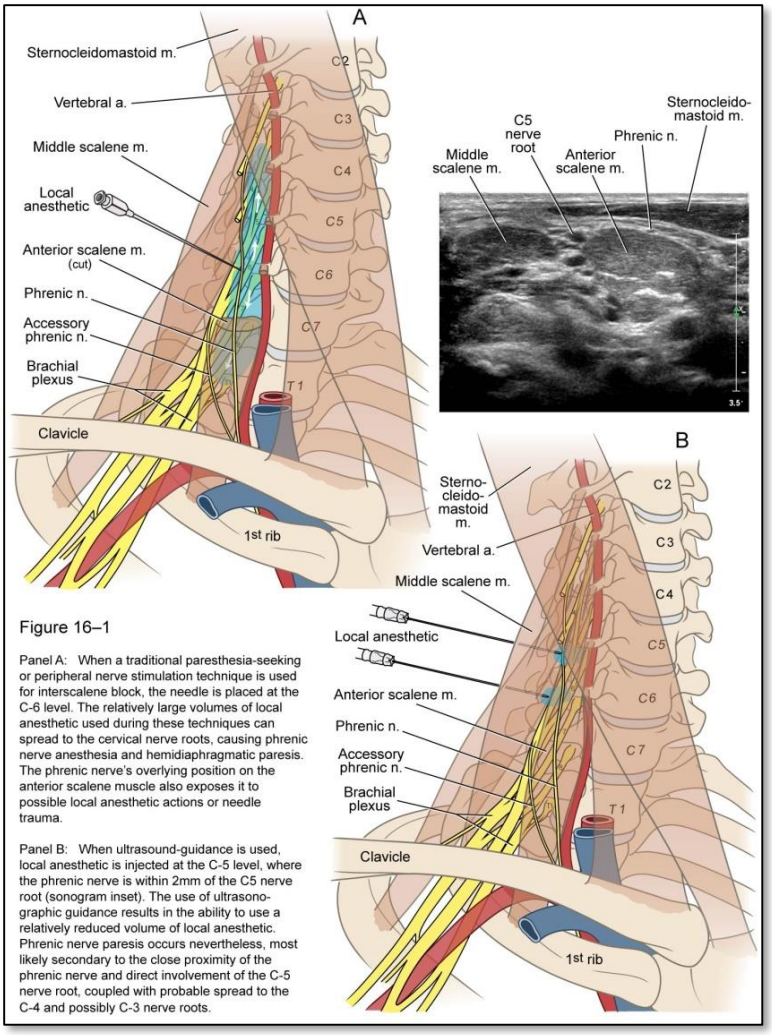

Figure 16–1

Panel A: When a traditional paresthesia-seeking or peripheral nerve stimulation technique is used for interscalene block, the needle is placed at the C-6 level. The relatively large volumes of local anesthetic used during these techniques can spread to the cervical nerve roots, causing phrenic nerve anesthesia and hemidiaphragmatic paresis. The phrenic nerve's overlying position on the anterior scalene muscle also exposes it to possible local anesthetic actions or needle trauma.

Panel B: When ultrasound-guidance is used, local anesthetic is injected at the C-5 level, where the phrenic nerve is within 2mm of the C5 nerve root (sonogram inset). The use of ultrasonographic guidance results in the ability to use a relatively reduced volume of local anesthetic. Phrenic nerve paresis occurs nevertheless, most likely secondary to the close proximity of the phrenic nerve and direct involvement of the C-5 nerve root, coupled with probable spread to the C-4 and possibly C-3 nerve roots.

Figure 4. Neal & Rathmell, 2013

Peripheral Nerve Injury

The use of an interscalene block does not increase the baseline risk of nerve injury associated with total shoulder arthroplasty. Permanent peripheral neuropathy associated with brachial plexus block is a decidedly rare event (95% confidence interval, 0–16 / 10,000 patients). Depending on how it is defined, temporary nerve dysfunction in the early postoperative period may occur in up to 19% of patients and typically presents within the first 48 hours. Most symptoms resolve by 6 weeks; well less than 0.1% remain after a year. Up to 10% of upper extremity elective orthopedic surgery patients will experience a transient (and rarely, permanent) injury inherent to the surgical procedure itself. When a patient sustains a peripheral nerve injury after brachial plexus block it is crucial the anesthesiologist recognize that the vast majority of these incidents are related to surgical factors—direct nerve trauma, positioning injury, stretch injury, or compressive etiologies from hematoma, edema, or the application of constrictive tourniquets, casts, or dressings. When motor function is impaired, the injury appears to be progressive, or improvement is not obvious after a few postoperative days, early neurological consultation is advised. Although abnormalities on neurophysiologic studies (EMG, nerve conduction studies) are most apparent 2 to 3 weeks after injury, earlier evaluation may be beneficial when injuries meet the above noted criteria. Early, bilateral neurologic evaluation may establish baseline, document pre-existing conditions, or identify reversible lesions.

Factors associated with anesthesia-related peripheral nerve injury are poorly understood. No human data exist to guide our choice of short- vs. long-beveled needles in preventing injury. The relationship of paresthesia elicitation to peripheral nerve injury is equally unclear. Pain on injection of local anesthetic is generally regarded as a sign of

potential nerve damage, but case reports suggest that this is an inconsistent warning sign. Not all pain on injection is associated with clinical injury. In contrast, there are reports of injury occurring when pain on injection was immediately followed by discontinuation of injection, implying that even if a warning occurs, the damage may already be done. There is no evidence that using UGRA reduces the incidence or severity of nerve injury, but there are case reports of injury despite the use of ultrasound. Two risks specific to brachial plexus regional anesthesia deserve comment. Reports of intramedullary spinal cord injection during interscalene block under general anesthesia while using the classic interscalene groove approach suggest that this practice may be dangerous. Furthermore, reports of peripheral nerve injury after supplemental selective nerve block performed at the elbow or wrist in patients with incomplete proximal brachial plexus blockade suggest that this practice too may be risky. There are no data to confirm or refute the contention that UGRA can reduce these risks.

In the absence of those rare instances when a needle fully or partially transects a nerve, anesthesia-related nerve injury is believed to result from a combination of factors. First, harmful needle contact or intrafascicular (subperineurium) injection damages the nerve-blood barrier. Once this protective barrier is breached, normally innocuous local anesthetics can cause neurotoxicity, which in turn can be worsened if epinephrine impairs clearance of local anesthetic from the perineural area and/or causes ischemia to the injured nerve. (Figure 5) Peripheral nerve injury may also occur in the setting of a 'double crush' phenomenon. This theory suggests that when nerves already compromised by an existing subclinical injury, e.g., cervical disc disease, diabetes mellitus, or neurotoxic chemotherapy, are then exposed to a second relatively minor injury, e.g., surgical positioning or a minor needle injury, significant clinical injury becomes manifest. There is clinical evidence to both confirm and refute the role of "double crush" in peripheral nerve injury. Finally, the brachial plexus is particularly prone to inflammatory neuropathies such as neuralgic amyotrophy. We inadequately understand these rare and usually temporary, but occasionally devastating, peripheral nerve injuries associated with brachial plexus regional anesthesia.

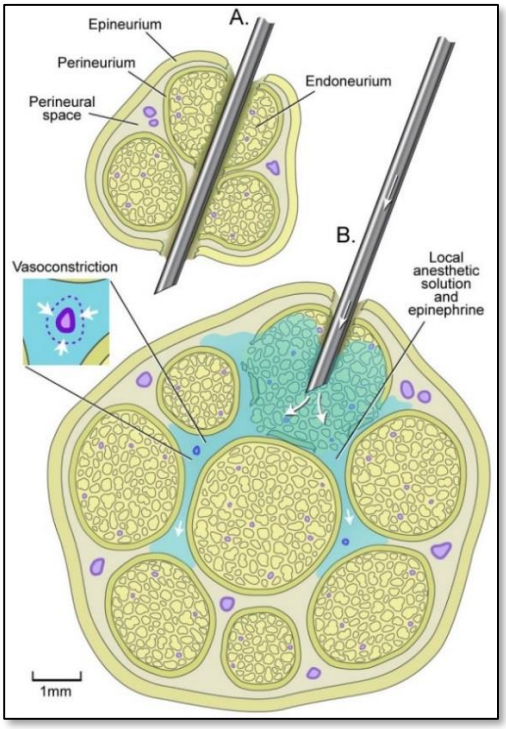

Figure 5. Neal & Rathmell, 2013

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ANESTHESIOLOGY 2017
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Highlights in Cardiac Anesthesiology: implications for us all

John G. Augoustides MD, FASE, FAHA **Philadelphia/Pennsylvania**

Introduction

The highlights in cardiac anesthesiology during the past year begin with the rapid progress in valvular heart disease, especially in the realm of transcatheter valve therapies. The ongoing clinical success in transcatheter aortic valve replacement has resulted not only in the evolution of this intervention as a mainstream therapy but its application in lower risk patients with aortic stenosis. Furthermore, the advent of transcatheter valve platforms for repair and replacement is already a clinical reality for selected patients with mitral, tricuspid and pulmonary valve disease. The second highlight in cardiac anesthesiology has been the further refinement in the management of coronary artery disease with major trials in both percutaneous coronary intervention and coronary artery bypass grafting. The third highlight in cardiac anesthesiology has encompassed the advances in the medical and mechanical management of heart failure with a new guideline, new drugs and new devices. The fourth highlight in cardiac anesthesiology has been the set of recent high-quality randomized trials exploring the outcome effects of perioperative steroids and statins in adult cardiac surgery. The following sections explore these highlights in further detail.

1. Valvular Heart Disease

The revolution is transcatheter aortic valve replacement (TAVR) has been dramatic since this procedure entered clinical practice in 2002.[1-2] Within the first decade thereafter, large trials resulted in commercial approval for these valves both in Europe and the United States and subsequently worldwide. There are essentially two types of valves currently in practice for TAVR: balloon-expandable valves and self-inflating valves.[2-3] These valves can be delivered safely and precisely to the aortic valve position via a number of arterial access routes, most commonly via transfemoral access.[2-3] The valve types and access route options have been reviewed in detail already elsewhere.[2-3]

There have been three major paradigm shifts in the evolution of TAVR practice in the last decade. The first paradigm shift was the establishment of TAVR as a safe and effective alternative to surgical aortic valve replacement for severe aortic stenosis not only in patients at excessive perioperative risk but also in patients at high perioperative risk, defined as a risk of perioperative mortality > 8% as calculated by the Society of Thoracic Surgeons score. The second paradigm shift has resulted from the recent high-quality trials that have established TAVR as a safe and effective alternative to surgical aortic valve replacement in intermediate-risk patients, defined as a risk of perioperative mortality in the range of (4-8)%, as calculated by the Society of Thoracic Surgeons risk score.[1-4] The latest data from these trials has resulted in a Class IIa recommendation for TAVR in symptomatic severe aortic stenosis from the 2017 valvular heart disease guideline from the American Heart Association (AHA) and American College of Cardiology (ACC).[5] In other words, the experts have recommended that TAVR is a reasonable therapeutic option in intermediate-risk patients with severe aortic stenosis, based on moderate quality evidence from randomized controlled trials (Level of Evidence: B – R).[5] The third paradigm shift is currently in progress, namely that TAVR could be a reasonable therapeutic intervention in low-risk patients with severe aortic stenosis, defined as a risk of perioperative mortality < 4%, as calculated by the Society of Thoracic Surgeons risk score.[1-2] There are large randomized trials currently in progress to evaluate this indication: their results will likely be available from late 2018 onwards (full details available at www.clinicaltrials.gov, last accessed June 28th 2017). In the 2017 AHA/ACC guideline, surgical aortic valve replacement is the only recommended intervention for low-risk patients with severe aortic stenosis, based on moderate quality evidence from non-randomized trials (Class I recommendation; Level of Evidence B – NR).[5]

The progress in TAVR continues in important subsets of patients with aortic stenosis. A large recent registry trial has also demonstrated that TAVR is safe and reasonable in bicuspid and tricuspid aortic valves, especially with the latest generation of valve technologies.[6] This is an important finding, since the major TAVR trials excluded bicuspid aortic valve stenosis due to concerns about anatomical variations. Given that bicuspid aortic valve is common, this latest dataset further increases the impact of TAVR in aortic stenosis.[5-6] The imperative to evaluate the therapeutic role of TAVR in moderate aortic stenosis has been highlighted by a recent observational trial in the setting of patients with moderate aortic stenosis (defined as aortic valve area 1.0 cm^2 -1.5 cm^2) and left ventricular systolic dysfunction (defined as an ejection fraction from 20% -50%).[7] In this trial, adverse clinical

outcomes were common at 4-year follow-up: all-cause death or hospitalization for heart failure was 48%; all-cause death was 36%; aortic valve replacement occurred in 24%; and, hospitalization for heart failure occurred in 27%. The independent predictors for these adverse outcomes were male gender, New York Heart Association functional class III/IV, and higher transaortic velocity.[7] These findings have prompted the randomized evaluation of TAVR in this high-risk population in the TAVR UNLOAD trial.[8] In the perioperative arena, further trials should evaluate TAVR as a preoperative intervention in patients with significant aortic stenosis who require elective major non-cardiac surgery, given that this valve lesion imparts high perioperative risk in non-cardiac surgery.[9]

Besides advances in bicuspid valve morphologies and moderate aortic stenosis, the conduct of TAVR has also focused on frailty as an outcome determinant and the evolution of anesthetic technique. Frailty is a geriatric syndrome that impairs resiliency to stressors to confer a high risk of adverse outcomes after invasive procedures.[10-11] Recent trials, including large clinical registries and meta-analyses, have demonstrated that frailty is a significant predictor of mortality after TAVR, suggesting that this health condition be included by the multidisciplinary heart valve team in the preprocedural risk assessment.[10-12] This comprehensive approach to patient selection by a multidisciplinary heart valve team has been emphasized in the 2017 ACC/AHA guideline (Class I recommendation; Level C evidence).[5]

The anesthetic for TAVR has also evolved steadily away from general endotracheal anesthesia with full invasive monitoring towards monitored anesthesia care with less invasive monitoring.[13] This evolution of anesthetic technique has been facilitated by multiple factors such as advances in TAVR hardware, less reliance on intraoperative transesophageal echocardiography, heart team experience, and the rarity of major complications.[13]Although there are no major randomized trials to compare TAVR outcomes as a function of anesthetic technique, recent meta-analysis has suggested that the major outcomes appear equivalent.[13-14] If monitored anesthesia care is chosen, it appears to proceed best in the setting of a mature program with an experienced team who have designed a perioperative pathway for these cases that includes screening criteria, a sedation protocol, and fast-tracking of postoperative care.[13-15] The continued progress in this therapeutic arena has established TAVR as a mainstream therapy for aortic stenosis in the setting of a multidisciplinary heart team model that includes the anesthesiologist.[16-17]

Given this spectacular success in aortic valve disease, transcatheter valve therapies have now been expanded to include the mitral, tricuspid and pulmonary valves.[5] Transcatheter mitral valve repair has been recommended in selected patients with severe mitral regurgitation and with excessive perioperative risk for surgical mitral valve intervention (Class IIb recommendation; Level of Evidence B).[5] In the setting of severe bioprosthetic valve dysfunction such as stenosis or regurgitation, a transcatheter valve-in-valve procedure has been recommended as a reasonable alternative to surgery in high-risk patients (Class IIa recommendation; Level of Evidence B – NR).[5] There is now considerable interest in the development of transcatheter platforms both for repair and replacement in tricuspid valve disease, especially for functional tricuspid regurgitation, given that it is the most common in the developed world.[18-19] These significant extensions of transcatheter valve therapy will likely further transform the perioperative assessment and management of valvular heart disease in the near future, as further platforms reach clinical practice. This paradigm shift in valvular heart disease will include the anesthesiologist both for anesthetic care and precise imaging guidance with real-time echocardiography, including three-dimensional technology as a vital adjunct for clinical decision-making during these challenging procedures.[20-23]

2. Coronary Artery Disease

Anniversaries such as the advent of ether anesthesia (October 16th 1846) and coronary artery bypass grafting (CABG - May 1967) offer the opportunity to reflect on medical innovation. It has been 50 years since Rene Favaloro performed his first CABG procedure on May 9th 1967 at the Cleveland Clinic.[24] Within 3 years, Dr Favaloro and his colleagues had performed more than 1000 of these procedures to usher in the surgical revolution for the management of ischemic heart disease.[24] The adoption of CABG throughout America was rapid thereafter with CABG volume per year surpassing 100 000 cases by 1977 and 600 000 by 1997.[24] The advent of CABG into clinical practice also provided a vital precedent for the development of coronary angioplasty by Andreas Gruntzig in 1976, given that the first cases were undertaken in the cardiac operating room.[24-5] Despite the 50th anniversary of CABG, the optimal conduct of this operation continues to be explored.

The typical surgical approach in CABG for multivessel disease is to anastomose the left internal mammary artery to the left anterior descending artery and to bypass coronary lesions elsewhere with either saphenous-vein or radial-artery grafts.[26] The single mammary-artery graft has an angiographic patency rate greater than 90% at 10 years, as compared with 50% for saphenous-vein grafts.[26-27] The excellent outcomes with single mammary-artery

grafts have prompted interest in CABG with bilateral mammary-artery grafts.[26-27] This approach has not been widely adopted due to the following issues: it adds complexity to the CABG procedure; it carries a higher risk of sternal wound complications due to the compromised sternal blood supply; and, there is a paucity of high-quality data to support this practice.[26-27] The Arterial Revascularization Trial was launched in 2004 to address these concerns, randomizing over 3000 CABG patients to single or bilateral mammary-artery grafts in 28 hospitals from 7 countries.[28] At one year, major clinical outcomes such as mortality, stroke, myocardial infarction and repeat revascularization were equivalent in both surgical cohorts, except for a small absolute increase of 1.3% in the requirement for sternal reconstruction in the bilateral mammary-artery cohort.[28] The 5-year clinical outcomes from this important randomized controlled trial were recently reported.[29] In summary, the bilateral mammary-artery technique at 5 years increased the risks for sternal wound complications (3.5% vs 1.9%: P = 0.005) and sternal reconstruction (1.9% vs 0.6%: P = 0.002) with equivalent risks for mortality (hazard ratio 1.04; 95% confidence interval 0.81 – 1.32; P = 0.77) and a composite outcome including death, stroke and myocardial infarction (hazard ratio 0.96; 95% confidence interval 0.79 – 1.17; P = 0.69).[29] Although the goal is to provide follow-up at 10 years, it already appears that bilateral harvesting of the mammary artery offers no outcome advantage with increased risks for sternal complications.[28-29]

A second debate in the conduct of CABG has been the role of cardiopulmonary bypass.[30-31] The CABG Off or On Pump Revascularization Study randomized 4572 patients from 70 medical centers in 10 countries to off-pump or on-pump CABG with tracking of the major clinical outcomes such as mortality, stroke, myocardial infarction, renal failure, and repeat coronary revascularization (either with CABG or percutaneous coronary intervention (PCI)).[30-31] At 30 days in this trial, off-pump CABG reduced the risks for bleeding, transfusion, respiratory complications, and acute kidney injury but increased the risk for early repeat revascularization (hazard ratio 4.01; 95% confidence interval 1.34 – 12.0; P = 0.01) with equivalent risks for death, stroke, myocardial infarction and dialysis.[30] At 1 year in this trial, there was a trend for increased risk for repeat revascularization (hazard ratio 1.66; 95% confidence interval 0.95 – 2.89; P = 0.07) in the off-pump cohort, with equivalent outcomes for death, stroke, neurocognitive dysfunction, myocardial infarction, dialysis, and quality of life.[31] The 5 year outcomes for this landmark randomized controlled trial were recently reported.[32] At 5 years in this trial, off-pump as compared to on–pump CABG was associated with equivalent outcomes death, stroke, neurocognitive dysfunction, myocardial infarction, renal failure, quality of life and overall costs.[32] This high-quality trial is the largest randomized trial to report longer term clinical outcomes in CABG as a function of cardiopulmonary bypass. Although further follow-up from this trial is ongoing, these two techniques for CABG appear ultimately equivalent with outcome differences in the short-term as outlined.

A third debate in the conduct of CABG has been the application of antifibrinolytic agents to reduce bleeding, transfusion and improve major clinical outcomes. Aprotinin has already been evaluated in this setting.[32-33] The lysine analogues, aminocaproic acid and tranexamic acid, have continued to be applied for limiting bleeding and transfusion in CABG where aspirin exposure is common, although concerns with tranexamic acid include seizures and prothrombotic complications.[34] In an attempt to address these concerns, the Asprin and Tranexamic Acid for Coronary Artery Surgery was launched as multicenter double-blinded clinical trial in which patients for CABG were randomized to aspirin vs placebo and tranexamic acid vs placebo.[35-36] In the aspirin arm of the trial, the aspirin dose was 100 mg and the cohort size was 2100 patients.[35] The primary outcome of interest was defined as a composite of death and thrombotic complications (nonfatal myocardial infarction, stroke, pulmonary embolism, renal failure, or bowel infarction) within the first 30 days after surgery. In this trial, aspirin exposure as compared to placebo nether increased the risk of the primary outcome (relative risk 0.94; 95% confidence interval 0.80 – 1.12; P = 0.55) or major hemorrhage requiring reoperation (P = 0.75).[35] In the tranexamic acid arm of this important trial, the initial dose of tranexamic acid was 100 mg per kilogram; the dose was subsequently reduced to 50 mg per kilogram to reduce the risk of seizures but still to preserve effective antifibrinolysis.[36] The cohort size was 4631 patients who mostly underwent on-pump CABG (97% of total cohort). The primary outcome of interest was defined as a composite of death and thrombotic complications (nonfatal myocardial infarction, stroke, pulmonary embolism, renal failure, or bowel infarction) within the first 30 days after surgery.[36] In this trial, exposure to tranexamic acid as compared to placebo did not increase the risk of the primary outcome (relative risk 0.92; 95% confidence interval 0.81 – 1.05; P = 0.22), but did increase the risk of seizures (0.7% vs 0.1%: P = 0.002).[36] Furthermore, tranexamic acid reduced the risk of major bleeding requiring reoperation, including pericardial tamponade (1.4% vs 2.8%: P = 0.001).[36]

Despite this plethora of recent high-quality randomized trials that have significantly informed the conduct of CABG, the search for optimal organ protection in this setting continues A recent large meta-analysis (N = 37

720: 13 studies) has suggested that for high-risk patients, minimal aortic manipulation during CABG significantly reduces the risk of stroke.[37] Further trials will likely explore this aspect of the operation in high-risk patients. In a similar fashion to the innovation and quality process evident in the maturation of CABG, the search for outcome improvement is evident in coronary revascularization with PCI. The recent major trials in this area will now be reviewed to understand better the evolving practice of PCI in its fifth decade as its dynamic relationship to perioperative practice is important both for cardiac and noncardiac surgery.

An ongoing debate in complex coronary revascularization concerns the ideal indications for CABG vs PCI in subpopulations such as left main coronary disease and non-ST elevation acute coronary syndromes.[37-38] Although CABG has been the benchmark for the management of left main coronary artery disease, the role of PCI has been evaluated in certain high-risk subgroups, including anatomically complex disease.[37] A recent meta-analyis (N = 4700: 8 randomized trials) was performed to suggest which strategy is optimal in this setting. In this analysis, clinical outcomes from the randomized trials of interest were classified by anatomical complexity of left main disease according to the established SYNTAX score and length of follow-up (early: up to I year; late: 3 – 5 years).[37; 39] The primary outcome of interest was defined as a composite of all-cause mortality, myocardial infarction, or stroke (major adverse cardiac events). The secondary outcome of interest was defined as a composite of major adverse cardiac events and repeat revascularization. Although composite outcomes were overall equivalent in this meta-analysis, CABG was associated with a higher risk of early stroke while PCI was associated with a higher risk of the secondary outcome at late follow-up in the setting of complex left main coronary anatomy.[37] In summary, this hypothesis-generating meta-analysis has suggested that CABG is preferable in highly complex left main disease, assuming reasonable perioperative risk. Based on this analysis, PCI appears to be a reasonable alternative to CABG in the setting of left main disease with low or moderate anatomical complexity.[37]

A second meta-analysis (N = 1246: 3 randomized trials) was recently performed to investigate the outcome differences between CABG and PCI in patients presenting with non-ST-elevation acute coronary syndromes in the setting of left main or multivessel coronary artery disease.[38] In this analysis, the primary outcome was defined as a composite of all-cause mortality, stroke or myocardial infarction. During the median follow-up of 5 years, the primary outcome was significantly reduced with CABG (hazard ratio 0.74; 95% confidence interval 0.56 – 0.98; P = 0.036), despite the fact that PCI was performed with drug-eluting stents. Furthermore, CABG was associated with a significantly lower risk of repeat revascularization (hazard ratio 0.56; 95% confidence interval 0.41 – 0.75; P < 0.001).[37] In summary, this meta-analysis suggests that CABG is superior to PCI in patients with extensive coronary artery disease presenting as a non-ST-elevation acute coronary syndrome.

These meta-analyses provide guidance for defining the optimal indications for PCI, given the spectrum of clinical presentation and anatomical lesions in coronary artery disease.[37-39] In the setting of stable coronary artery disease, PCI may not always be appropriate, especially in the setting of intermediate lesions (40% - 80% stenosis).[40] The measurement of fractional flow reserve (FFR) during PCI for stable coronary artery disease has been demonstrated in multiple randomized trials to enhance detection of hemodynamically significant coronary stenoses for intervention with subsequent improved clinical outcomes.[40-41] The quantification of FFR is obtained during coronary catheterization in which the pressure drop is measured across the coronary lesion of interest at rest and again during pharmacologically induced hyperemia with a vasodilator such as adenosine. The current evidence base clearly has demonstrated that coronary stenosis with normal FFR measurements can be managed medically with no adverse outcome risk.[40-41] Despite strong supporting data, the clinical adoption of FFR has remained low due to concerns about cost, increased procedural time, and significant adverse effects such as bradycardia, and heart block due to vasodilator administration.[40] The instantaneous wave-free ratio (iFR) has been recently evaluated as an alternative to FFR, given that its measurement does not require administration of a vasodilator during pressure determinations across a coronary lesion. The iFR is measured as the pressure drop across the coronary lesion of interest during the wave-free phase of late diastole with specially designed coronary-pressure guidewires. Two recent large randomized trials (total N = 4529) have both demonstrated equivalent outcomes at 1 year in PCI for intermediate coronary lesions assessed with either of FFR or iFR.[42-43] A major advantage of iFR in both these trials was that it was associated with significantly reduced procedural adverse effects and a shorter procedural time due to the waived requirement for administration of a vasodilator.[42-43] In the setting of stable coronary disease, PCI is typically performed for control of angina: in this setting, these trials suggest that iFR could replace FFR for guidance of PCI in intermediate lesions. This technology does not apply to PCI in acute coronary syndromes, where current evidence supports early PCI based on anatomical assessment of lesion severity.[41] Future trials will likely explore whether non-invasive techniques could replace iFR during coronary angiography for simultaneous assessment of anatomical and physiological assessment of coronary lesions, thereby avoiding the need for coronary catheterization.

The evolution of coronary stents has been major advance through the five decades of PCI since the first coronary angioplasty by Dr Gruntzig in 1976.[25; 44-45] The bare metal and drug-eluting stents significantly reduced the risk of coronary restensosis after balloon angioplasty. Despite all their advantages, the current second-generation drug-eluting stents still have limitations such as a late thrombosis risk, prevention of optimal arterial remodeling and interference with future CABG.[44-45] These disadvantages are largely a result of their metallic structure that results in a permanent coronary implant. The advent of the first generation of bioresorbable stents have offered the possibility of overcoming these limitations, given that they degrade over time in the coronary artery to leave no residual implant.[44-45] Although the bioresorbable everolimus-eluting coronary stent has achieved commercial approval after demonstrated equivalency to conventional drug-eluting stents, recent data from randomized trials and meta-analyses have suggested that the risk of late thrombosis is significant.[44-46] Given this higher risk of thrombosis associated with the first generation of drug-eluting bioresorbable stents, there is little incentive to apply this technology further in clinical practice until further design improvements to maintain coronary patency while still undergoing ultimate bioresorption.[44-45] In the interim, patients with these coronary stents would likely benefit from extended dual antiplatelet therapy both in the ambulatory and perioperative setting.[47-48]
In summary, the interventional management of coronary artery disease continues to evolve since advent of CABG in 1967 and PCI in 1976. In the conduct of CABG, recent high-quality clinical have refined the approaches with vascular conduit such as the internal mammary artery, the role of cardiopulmonary bypass, the application of antifibrinolytics, and the role of aortic manipulation in patients at high-risk for stroke. In the conduct of PCI, high-quality data has also refined the indications for PCI in complex coronary artery disease, the functional assessment of intermediate coronary lesions, and the integration of first generation bioresorbable coronary stents. All these advances have likely contributed to the falling risk of perioperative myocardial ischemia in non-cardiac surgery, although further trials should continue to investigate perioperative protection not only of the myocardium but also the brain: although there are some showers, it is mostly sunny.[49-50]

3. Heart Failure

The recent advances in the understanding of heart failure have prompted a 2017 ACC/AHA guideline update for the management of heart failure.[51] The first management update highlighted in this guideline is that the measurement of natriuretic peptide biomarkers such as B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) can assist the prevention, diagnosis, severity classification, and prognosis of heart failure.[51] As a consequence of this maturation of the clinical utility of these biomarkers, further trials will likely explore the role of BNP and NT-proBNP in the management of heart failure in the perioperative period. The second management update from this 2017 guideline is that the inhibition of the renin-angiotensin system in a systematic fashion significantly reduces morbidity and mortality in chronic heart failure with reduced ejection fraction (HF-rEF).[51] This inhibition can be achieved with titration of an angiotensin-converting enzyme inhibitor (ACE), or an angiotensin receptor blocker (ARB) or an ARB combined with a neprilysin inhibitor (ARNI) such as valsartan/sacubitril.[51] Neprilysin is an enzyme that degrades vasoactive peptides such as BNP, bradykinin, and adrenomedullin. The risk of therapy with ARNI include hypotension, renal insufficiency and angioedema.[51] The entrenchment of systematic inhibition of the renin-angiotensin system with ACE, ARB and/or ARNI in heart failure patients will likely increase their risk of hypotension in the perioperative period that will require meticulous management.[52-53]

The third management update from this guideline is that in selected patients with symptomatic chronic HF-rEF who are receiving guideline-directed management and therapy, the addition of ivabradine can significantly reduce hospitalizations for exacerbations of heart failure.[51] Ivabradine is a novel agent that selectively inhibits the I_f current in the sinoatrial node to reduce heart rate with no negative inotropic effect.[51;54] The fourth management update from this important guideline covered 3 significant comorbidities in heart failure, namely anemia, hypertension and sleep disordered breathing.[51] In the setting of anemia and heart failure, intravenous iron rather than erythropoietin may improve functional status in selected patients.[51] In the setting of hypertension and heart failure, vasodilator titration should aim for a systolic blood pressure below 130 mmHg, assuming that volume overload has been addressed.[51] In the setting of heart failure with sleep disordered breathing or excessive daytime sleepiness, referral for formal sleep assessment is reasonable. Furthermore, in patients with cardiovascular disease and obstructive sleep apnea, therapy with continuous positive airway pressure is reasonable to enhance sleep quality and reduce daytime sleepiness.[51]

The optimal management of heart failure includes guideline-driven management and therapy, as outlined by the 2017 ACC/AHA guideline.[51] Beyond optimal medical therapy, refractory heart failure may require

mechanical support and/or heart transplantation. This year marks the 50th year since the first successful heart transplant was performed in Cape Town on December 3rd 1967 by the heart team led by Dr Christian Barnard.[55-56] The ability to conduct this successful cardiac anesthetic with the limited facilities, monitoring and drugs available in 1967 attests to the considerable skill of the anesthesia team led by Dr Joseph Ozinsky.[55-56] During the 1970's heart transplantation was still limited to a handful of centers around the world, but with the introduction of cyclosporine in the 1980s, heart transplantation subsequently generalized and matured into a mainstream therapeutic option for advanced heart failure.[55-57]

Despite the major clinical success with heart transplantation around the world, the demand for mechanical alternatives has prompted the ongoing refinement of the left ventricular assist device (LVAD).[58] Despite the improved clinical outcomes offered by the axial-flow design as compared to the older pulsatile LVAD technology, a significant risk of LVAD thrombosis has prompted an ongoing search for third generation technology to further enhance safety and efficacy of the LVAD.[59-61] A recent randomized trial evaluated a new centrifugal-flow LVAD with the axial-flow LVAD as a study control.[62] This third generation device is smaller and lies within the pericardial space due to its bearingless design that includes magnetic and hydrodynamic levitation of the internal rotor (HeartWare LVAD, HeartWare International, Framingham, Massachusetts, USA).[62] This multicenter trial randomized 446 patients in a 2:1 ratio to the study device (centrifugal-flow) or the control device (axial-flow). The primary endpoint of this non-inferiority trial was defined as survival at 2 years with freedom from disabling stroke or device removal for malfunction or failure.[62] In summary, the primary endpoint was found to be non-inferior in both study groups (P = 0.01 for non-inferiority), although more patients in the study group had strokes (29.7% vs 12.1%) and more patients in the control group had serious device failure requiring replacement (16.2% vs 8.8%).[62]

A second randomized trial evaluated a centrifugal-flow HeartMate 3 LVAD (St Jude Medical;, Little Canada, Minnesota, USA) compared to the axial-flow HeartMate 2 LVAD (St Jude Medical;, Little Canada, Minnesota, USA).[63] The engineering features of the centrifugal-flow HeartMate 3 LVAD include wide-flow blood passages, no mechanical bearings, low friction, and an intrinsic artificial pulse. These features were selected to reduce shear stress on blood elements and minimize the risk of pump thrombosis.[63] This trial randomized 294 patients to either the HeartMate 3 or the HeartMate 2 device. The primary endpoint of trial was defined as a composite of survival with freedom from disabling stroke or device removal/replacement at 6 months. In summary, the primary endpoint was found to be significantly lower in the HeartMAte III group (76.8% vs 86.2%; hazard ratio 0.55; 95% confidence interval 0.32 – 0.95; P = 0.04 for superiority). The risk of reoperation for pump failure was significantly lower in the HeartMate III group (hazard ratio 0.08; 95% confidence interval 0.01 – 0.60; P = 0.002).[63] Taken together, these two landmark trials have likely ushered in the centrifugal-flow LVAD era, assuming that favorable clinical outcomes continue in the mid-to long-term.

The occurrence of heart failure after cardiac surgery with cardiopulmonary bypass has an estimated incidence of about 10% with more than a million patients undergoing such procedures every year in Europe and the United States.[64-65] Levosimendan is a calcium-sensitizing inotrope that is currently in clinical practice in more than 60 countries around the world for prevention and treatment of the low cardiac output syndrome after cardiac surgery.[64-66] Two recent landmark randomized trials have recently evaluated levosimendan for prophylaxis against this complication.[64-65] The first trial randomized 882 patients with an ejection fraction of 35% or less to either levosimendan or placebo during cardiac surgery with cardiopulmonary bypass.[64] The first primary endpoint was a composite of 4 outcomes: death at 30 days; renal replacement therapy at 30 days; myocardial infarction at 5 days; and, mechanical circulatory support at 5 days. The second primary endpoint was a composite of 2 outcomes: death at 30 days; and, mechanical circulatory support at 5 days.[64] In summary, exposure to levosimemdan did not reduce the risk of the 4-component primary outcome (adjusted odds ratio 1.00; 99% confidence interval 0.66 – 1.54; P = 0.98) or the 2-component primary outcome (adjusted odds ratio 1.18; 96% confidence interval 0.76 – 1.82; P = 0.45).[64] The second randomized trial randomized 506 patients with left ventricular failure to levosimendan or placebo during cardiac surgery with cardiopulmonary bypass with a primary endpoint defined as mortality at 30 days.[65] The trial was terminated for futility. Levosimendan exposure did not reduce the risk of the primary endpoint (absolute risk difference 0.1; 95% confidence interval -5.7 to 5.9; P = 0.97).[65] Furthermore, there were no significant differences with respect to hypotension, arrhythmias, duration of mechanical ventilation, as well length of stay in the intensive care unit or hospital.[65] Taken together, these 2 randomized trials do not support the application of levosimendan for outcome improvement in patients with heart failure after cardiac surgery.

4. Steroids and Statins

The promise of steroids and statins in cardiac surgery with cardiopulmonary bypass has been attractive, given their suppression of the perioperative systemic inflammatory response.[67] In the case of steroids, two large multicenter placebo-controlled randomized trials have demonstrated that these agents offer no outcome advantage in adult cardiac surgery. The first trial evaluated high-dose dexamethasone (1mg/kg: 100 mg maximum) in adult cardiac surgery at 8 medical centers across the Netherlands (N = 4494).[68] The primary outcome was defined as a composite of death, myocardial infarction, stroke, renal failure, or respiratory failure at 30 days. Exposure to dexamethasone did not reduce the risk of the primary outcome (relative risk 0.83; 95% confidence interval 0.67 – 1.01; P = 0.07).[68] The second trial evaluated high-dose methylprednisolone (total dose 500 mg) in adult cardiac surgery at 80 medical centers in 18 countries (N = 7507).[69] The defined primary endpoints were death at 30 days and a composite of death, stroke, myocardial injury, respiratory failure, or renal failure at 30 days. Exposure to methylprednisolone did not decrease the risk of death at 30 days (relative risk 0.67; 95% confidence interval 0.70 – 1.07; P = 0.19) or the risk of the composite outcome (relative risk 1.03; 95% confidence interval 0.95 – 1.11; P = 0.52).[69] Taken together, these landmark randomized trials do not support the routine application of steroids in adult cardiac surgery with cardiopulmonary bypass. Further high-quality trials are indicated to evaluate the role of steroids in pediatric cardiac surgery with cardiopulmonary bypass.

In the case of statins, a large recent meta-analysis of randomized trials in cardiac surgery (N = 5102: 23 trials) has demonstrated that statins are not protective against mortality, stroke, myocardial infarction, atrial fibrillation, and infection.[70] Furthermore, this meta-analysis has suggested that statins may be associated with an increased risk of acute kidney injury (odds ratio 1.25; 95% confidence interval 1.05 – 1.52; P = 0.01).[70] This lack of perioperative benefit has also been confirmed in a subsequent large meta-analysis.[71] The current evidence base suggests that statins are not a magic bullet to improve major clinical outcomes after adult cardiac surgery. Further trials should explore the safety and optimal management of these agents in the perioperative seting.[72]

Conclusions

There has been significant recent progress in perioperative cardiovascular practice across the domains of valvular heart disease, coronary artery disease, heart failure, and medical manipulation of the systemic inflammatory response. Taken together, these advances will likely enhance the safety and clinical outcomes for our patients.

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ANESTHESIOLOGY 2017
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"IEDs (Improvised Explosive Devices): What Every Anesthesiologist Should Know".

Michael J Murray MD PhD **City/State: Danville, PA**

Introduction: Improvised Explosive Devices (IEDs) have proven to be the device of choice for insurgents and terrorists. They are inexpensive, easily concealed and can result in significant morbidity and mortality – 9/11, the Oklahoma City Bombing, the Boston Marathon Bombing, the more recent Ariana Grande Concert bombing etc. In 2012 there were over 16,000 IEDs used by the Taliban in Afghanistan against coalition forces, and a cursory review of the media underscores the fact that they are the weapons of choice used by terrorists, though automatic weapons such as rifles, and even vehicles driven into crowds have been successfully used. IEDs however, are most worthy of review because they injure via three different mechanisms – via the blast itself, penetrating injury from projectiles and/or from blunt trauma. A recent survey of anesthesiologists found that a majority thought that they were unprepared for a mass casualty incident or event. The anesthesiologist who is familiar with the management of casualties caused by IEDs will be well prepared to manage patients in their daily practice injured by industrial explosions, gunshots or blunt trauma sustained in a motor vehicle crash.

Explosions: IEDs usually have compounds that contain nitrogen and oxygen such as ammonium nitrate, potassium nitrate (gunpowder) trinitrotoluene (TNT), cyclotrimethylene-trinitramine (explosive material in C-4) etc. The presence of oxygen in the molecule allows an extremely rapid oxidation-reduction reaction to occur in the presence of an appropriate ignition source. The chemical reaction is extremely exothermic and produces an incredible amount of combustion gases in a very short period of time measured in milliseconds. The gases that are produced create a huge increase in pressure at the site – and as these gases expand radially outward from the site they produce shock waves that are the *sine que non* of an explosion. Propagating shock waves obey the laws of physics and therefore, have a positive phase and a negative phase, and in addition, as heat is dissipated from the explosion the surrounding air molecules are heated and create a third component of the blast – blast wind. The destructive power of a blast is related to the degree of overpressure of the initial shock wave along with the duration of the wave; further damage can occur when the negative phase occurs, a phenomenon that commonly effects buildings for example.

Mechanism of Injuries: Traditionally, injuries from blasts are categorized as primary, secondary, tertiary and quaternary (or combination) injuries.
Primary blast injuries occur from the propagating shock wave as it impacts fixed objects. The amplitude of the increased ambient pressure and the duration of the overpressure correlate with the degree of destruction. For living organisms, the energy contained in the blast wave is transmitted to and propagated across biologic tissue. Human tissue or organs containing air are especially susceptible to injury such as the middle ear, intestines and lungs as when air contracts and expands it can rupture tympanic membranes, alveoli and the colon. However, solid organs can also sustain significant injury as evidenced by the number of individuals who sustain traumatic brain injury and traumatic amputations following detonation of an IED.
Secondary blast injuries: IEDs are commonly made by placing the explosive material in a metal container along with items such as ball bearings, nails, pieces of metal etc. Following detonation, the metal container ruptures, and the metal, along with the contents of the device are propelled outwards with the blast wave becoming high speed projectiles that are capable of causing penetrating injury.
Tertiary blast injuries: As the blast wave moves radially outward from the point of detonation, objects in its path are exposed to this injury. Depending on the amount of energy, a human in its path can be blown into a building or other immovable object, and sustain blunt trauma. Alternately, if the blast is powerful enough, the building or immovable object can collapse on top of bystanders causing blunt trauma.
Quaternary Injuries: A term not used by all, quaternary or combination injuries are those caused by a combination of mechanisms outlined above, or as the term is most frequently used, it refers to those injuries caused by one of the mechanisms described above and by another mechanism – thermal injury caused by the heat contained in the blast wave, or from radiation injury if for example, the IED contains radioactive material, a so called "dirty bomb." A healthcare worker who sustains a myocardial infarction as a result of the stress associated with the blast or the work of extracting others from collapsed buildings.

Treatment

Following the Boston Marathon Bombing victims were treated at 29 different hospitals. From that knowledge we should conclude that though we may not work at a Level I trauma center we still might be in a situation either in the emergency department, in the operating room, or in the intensive care unit in which we may have to help manage many casualties who have sustained traumatic injury from an IED. Depending on the circumstances, we might be assigned to triage, and with many casualties arriving simultaneously, distinguishing who has sustained significant injury and who has not, is not always straightforward. 80-90 % of individuals who are closest to the explosion and at highest risk of injury will have traumatic rupture of their tympanic membranes. If the tympanic membranes are intact significant injury is unlikely. Following an otoscopic exam, measurement of oxygen saturation via a pulse oximeter and a quick abdominal exam should help rule out significant injury in patients who might worry about unrecognized injury.

The first steps in treating more seriously injured patients have been summarized by the U S Department of Homeland Security, and are similar to what the military trains all of its medics to implement when managing patients who have sustained blast injury. The first step, in an unconscious patient is placement of a nasal airway, which in ~ 1% of patients may be lifesaving. For those patients with significant bleeding tourniquets and hemostatic agents are efficacious in abating or preventing hemorrhage in patients with extremity injury (tourniquets) and other sites on which a tourniquet cannot be used (hemostatic agents). A third step in managing IED casualties is recognition and treatment of pneumothoraxes. Insertion of a pig tail catheter or even an intracath in the second intercostal space may be lifesaving.

Damage Control Resuscitation: Having performed triage in the emergency department, and cognizant of the injuries patients may have sustained, management of these patients is similar to the management of other patients who have sustained traumatic injury. Damage control resuscitation implies that the surgeon will control the bleeding as quickly as possible. From our perspective the use of crystalloid and vasoconstrictors should be limited to what is absolutely necessary. Patients who are hypotensive from hemorrhage should receive what has been and is being lost i.e. packed red blood cells, fresh frozen plasma, and platelets, or if necessary whole blood. While open to clinical judgment, the majority of patients receive a ratio of pRBCs:FFP:platelets of 1:1:1.

Managing Hypothermia

The association of hypothermia, acidosis and coagulopathy (the triad of death) with increased mortality has been well described. Therefore, the OR should be warmed to 85-90° F, fluid warmers should be used as should heated water blankets, and when possible forced air warming devices are used. For those patients at highest risk of developing acute traumatic coagulopathy should have coagulation status measured with a device that measures the functional integrity of the coagulation cascade on a real time basis.

Traumatic Brain Injury: Individuals who are injured by an IED are at risk of having TBI, even if there is no visible sign of injury to the cranium, again depending on the magnitude of the blast wave. This is especially true if there are mechanical factors that focus or direct the blast wave such as a helmet (soldier) or a narrow space between two buildings. Patients who are unconscious on arrival at the hospital should have an MRI, and if there is evidence of injury, should be managed as one would manage any patient with raised intracranial pressure.

Debridement

After the initial surgical procedures, wound debridement and irrigation (D&I) are the most frequently performed surgical procedure over subsequent days. Recommendations are for the wounds to be debrided at least every 2 days (or more often depending on the nature of the wound) to remove nonviable tissue, debris, blood and bacteria, which is important to prevent local and systemic complications associated with such a wound. While the goal is to remove all nonviable tissue, one tries to preserve as much soft tissue as possible for later reconstructive surgery. Following debridement the wounds are irrigated, typically with sterile isotonic solution (the fluid of choice for irrigation) using large volumes of fluid; bacterial loads drop logarithmically with increasing volumes of 1, 3, 6, and 9 liters of irrigation. Negative Pressure Wound Therapy with Reticulated Open Cell Foam (NPWT/ROCF) dressing, commonly referred to as a VAC dressing, is used to cover the wounds before transporting the patient from the OR.

Treating Infection:

Bacterial infections are major concerns and the most common cause of long term morbidity. Although definitive data do not exist, blast wounds are particularly susceptible to infection, and that the risk of infection (especially fungal infection) is greater when multiple limbs are involved. With every trip to the OR debrided tissue is sent to

the pathology department for microscopic examination for vascular invasion by fungi. Soldiers with evidence of invasion are treated aggressively with antifungal agents and with more frequent and aggressive debridement.

Conclusion: Over the last several years the use of IEDs by terrorists has increased significantly. As physicians we bear responsibility to educate ourselves and be prepared to manage patients who have sustained traumatic injuries following a mass casualty event in which an IED was used.

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The Centralization and Persistence of Postoperative Pain

David J. Clark, M.D./Ph.D. **Palo Alto, California**

Introduction

At this point the magnitude of the problem is becoming clear. Chronic pain affects nearly 25% of the US population, and the prevalence is 50% or greater within certain populations such as military veterans. The costs in terms of direct medical care and lost productivity total over 600 billion dollars per year [1]. An undefined but likely large percentage of this unfortunate group developed chronic pain after some form of trauma. Traumatic causes of chronic pain can be divided further according to their initial causes although the mechanisms supporting chronic pain have significant overlap as will be discussed in the course of the presentation. On-the-job injuries, motor vehicle accidents, sports-related injuries and surgery are all well-recognized causes of chronic pain. In each of these cases pain continues well past the time at which tissue healing would be expected to be complete. Why then does the pain problem persist and even spread to involve mood, cognition and other functions? The so-called centralization of pain whereby changes within the CNS support an ongoing pain state provides an important part of the answer to this vexing question.

Epidemiology of pain after surgery, costs

Chronic post-surgical pain (CPSP) is a common after surgery, and is in fact a common etiology of chronic pain in the general population. Although we may not have absolute consensus on the definition of CPSP, many reviews suggest that between 5 and 85% of patients experience pain that persists months after surgery. Most surgical procedures have some identifiable rate of CPSP with some, especially those in which nerve damage is common, having especially high rates. Limb amputation, thoracotomy, breast surgery and herniorrhaphy are amongst those procedures with the highest rates of CPSP. Cross-sectional analyses have suggested that more than 20% of patients with chronic pain could identify surgery as a causal factor [2]. Chronic pain such as chronic neuropathic pain from traumatic and surgical causes is immensely expensive. Recently the direct and indirect annualized costs for caring for these patients were estimated to be approximately $12, 000 and $30,000 respectively [3].

Pain resolves at rates specific to individual patients

The rate of resolution of pain after surgery is highly specific to the individual. A high level of variability in recovery rates is seen in major surgeries, e.g. joint replacement and minor procedures, e.g. carpal tunnel release, alike. For almost no form of trauma, operation or procedure does the fraction of patients with no pain drop to zero. Thus we might be best served in our efforts to understand persistent postoperative pain to examine processes governing the rate of resolution of pain in addition to identifying the very persistent changes that might explain chronic postoperative pain.

Within this framework we can identify processes that are clearly near-term and transient such as wound area processes. Factors relevant to the fist moments to days after surgery include the release of algogens, production of inflammatory mediators and infiltration of immune cells. Intermediate processes supporting pain may involve the production of trophic molecules supporting healing, sensitization and nerve regrowth into damaged tissues. Physical forces applied to healing tissue with simple movements like breathing or more forceful ones such as are involved in physical rehabilitation result in disruption and remodeling of the sensitized healing tissue. As the sometimes months long healing process nears completion, however, we are forced to look at more central changes to explain ongoing pain.

The need to separate persistent pain in the setting of adequate healing from ongoing pathology

Critical to the care of patients after injury who report ongoing pain is to rule out persistent or recurrent pathology. It is worth careful consideration in addressing any patient with delayed resolution of pain or certainly when evaluating worsening pain to consider the possibility that a complication arising from the surgery or trauma exists. Infection is a clear example of a secondary process that can affect superficial or deep tissues and enhance pain levels. Infection may not be obvious such as when a deep abscess or osteomyelitis is present. Appropriate physical examination, laboratory studies and imaging may be required. Additional causes of pain reflecting a tissue-level problem rather than a fundamental alteration in nociceptive signaling include fracture from intramedullary component placement, physical compression of nerves from misplaced staples or sutures, and adhesions in joints or soft tissue arising from immobilization. As each of these etiologies of pain has a distinct treatment approach, they need to be considered without delay.

Risk factors

Many risk factors for the development of CPSP have been identified with varying degrees of certainly, and attempts have been made to construct predictive tools [6, 7]. This area of investigation is being pursued actively as the identification of specific risk factors may shed light on mechanisms of CPSP, provide the means to construct risk stratification tools and suggest avenues for the prevention and treatment of this condition. The factors currently most strongly associated with CPSP are listed below. Additional contributors including genetic factors, immune system responsiveness and the efficacy of endogenous pain control systems are undergoing evaluation as well.

Perioperative pain – The existence of either preoperative or high levels of acute postoperative pain are relatively well-reproduced risk factors for chronic postoperative pain. Very recent evidence connects chronic wide-spread pain with CPSP via pathways involving the brain itself.

Psychological characteristics – Several psychological constructs have been associated with CPSP. Amongst the best studied and validated are depression, anxiety and catastrophizing.

Opioids – Patients consuming opioids preoperatively have substantially higher rates of acute and chronic postoperative pain. This association is not limited to a single type of surgery, but most studies have been performed in orthopedic and spinal surgery populations in which the proportion of patients taking opioids is relatively high.

Demographics – Demographic characteristics are very easily assessed, but widely reproduced associations have not been established. At least some evidence exists, however, for a protective effect of age and perhaps male sex on chronic pain after certain surgeries. A special set of considerations may apply to pregnant females as chronic pain after cesarean section has been noted to be particularly low.

Genetics and epigenetics – Less well studied perioperatively than for other chronic pain conditions, but strongly felt to impact acute and chronic pain.

Surgical technique – Performing surgeries in ways that speed recovery in general if not CPSP specifically has been a focus for the surgical community for some time. To this end, laparoscopic and nerve-protecting surgeries have been developed, and there is some evidence that for procedures such as herniorrhaphy, newer techniques might offer better pain outcomes. Longer surgeries may lead to higher rates of CPSP as well.

Is it just pain?

Chronic pain including but not limited to CPSP evolves to encompass problems separate from those related to nociceptive signaling and the experience of pain itself. Abundant evidence from psychophysical evaluations and imaging studies has demonstrated adverse effects of chronic pain on mood and cognition. To some extent these changes have been traced to multi-functional areas of the brain. Thus “centralization” of pain is a set of maladaptive changes with multiple dimensions. The suggestion has been made that the centralization of pain be defined as, “pain-induced changes in brain circuits resulting in altered/pathological behaviors” in order to capture the multi-

faceted nature of centralization [4]. Nociceptive drive may initiate these changes, but it is not clear that ongoing high levels of nociceptive input are required to maintain the maladaptations. Thus once established, therapies limited to peripheral targets may no longer be effective.

Imaging studies have shown that noxious input not only activates areas of the brain commonly associated with sensory function, e.g. the thalamus and somatosensory cortex, but also regions involved in emotions, e.g. the cingulate cortex and insula, pain modulation, e.g. the anterior cingulate cortex (ACC) and cognition, e.g. the ACC and prefrontal cortex. Similarly, imaging studies have shown a detrimental effect on hippocampal volume in patients with chronic back and limb pain [5]. Together the data indicate that brain-level activation of centers and circuits with pain, cognitive and emotional functions may explain the association of chronic pain with changes in executive function, memory, depression and anxiety.

The Centralization of Pain – Spinal: Secondary hyperalgesia, wind-up, synaptic efficiency, glia

The dorsal horn of the spinal cord is perhaps the best studied area of the CNS related to pain processing and analgesic mechanisms. A large body of information suggests that this area of the spinal cord is critical to central sensitization after noxious stimulation and injuries of many types [8]. Sensitization of the dorsal horn and enhancement of nociceptive signal transmission has been observed in association with peripheral nerve damage, inflammation, incision, tumor growth and other events. In association with spinally-mediated central sensitization we often observe secondary hyperalgesia, enhanced temporal summation and, of course, increased pain. Under some circumstances these changes are reversible, but sensitization outlasts the period of high intensity noxious stimulation and can be maintained by low levels of c-fiber input. These observations are in fitting with the idea that spinal sensitization might support persistent pain.

Key events driving central sensitization at the spinal level include 1) the enhancement of synaptic efficiency akin to the process of long-term potentiation (LTP) well-studied in the field of memory research. This enhancement derives from augmented neurotransmitter release from afferent neurons and increased excitability of second order neurons, 2) the activation of glial cells including astrocytes and microglia leading to the production of cytokines, neurotrophins and other mediators supporting the excitability of nociceptive neurons, and 3) the ability of formerly non-noxious input from low-threshold mechanoreceptors to activate nociceptive circuits thus providing a neurophysiological basis for allodynia. Understanding these processes also provides a basis for the hypothesis that the use of neural blockade, spinal anesthesia and NMDA receptor blockers might reduce spinal cord sensitization and speed the resolution of pain after injury.

The Centralization of Pain – Brainstem: Conditioned pain modulation, descending inhibition and facilitation

Nociceptive signal transmission and ultimately the experience of pain are regulated by many mechanisms including descending modulation. Descending modulation can be inhibitory or stimulatory. These systems are capable of modulating acute and chronic pain, although it is chronic forms of pain that clinically seem to have the strongest evidence for involvement of descending control. The principal modulatory systems include the noradrenergic system involving the locus coeruleus (LC) and the serotonergic system involving the rostral ventromedial medulla (RVM) [9]. The periaqueductal gray (PAG) is the primary control center for descending inhibition, and is a major site for the analgesic actions of endogenous and exogenous opioids. At the level of the spinal cord, norepinephrine controls nociceptive signal transmission through alpha-2 adrenergic receptors while serotonin acts through the 5-HT3 receptor and others to control the flow of nociceptive information. More recently the dopaminergic system has been implicated in regulating pain via descending inhibition targeting D1, D2 and D5 receptors [10].

Acute postoperative pain is poorly correlated with preoperatively assessed conditioned pain modulation (CPM) [11, 12]. More persistent forms of pain after injury may be more strongly regulated by these centers, however. For example, thoracotomy and abdominal surgery patients with more efficient CPM responses measured preoperatively were less likely to develop persistent postoperative pain. Simple measures of nociceptive thresholds were not predictive in the same way. Laboratory studies reflect and extend these observations. For example, Peters et al.

demonstrated that the rate of resolution of allodynia after nerve injury depended on descending noradrenergic input to the spinal cord. Intriguingly, preoperative conditioned pain modulation (CPM) correlated with the timecourse of postoperative resolution of mechanical hypersensitivity after spinal nerve ligation [13]. Persistent opioid administration is linked both to reduced net inhibitory control and enhanced levels of pain-related behaviors after incision and other forms of injury. Imaging studies have begun to suggest that descending inhibition is disrupted in various chronic pain states as well. These and other observations suggest that we may be able to predict delayed pain resolution preoperatively by measuring CPM, and that treatments enhancing descending regulatory circuits might be effective in controlling postoperative pain.

The Centralization of Pain – Cortical/Subcortical structures

The intense afferent barrage that accompanies surgical incision and manipulation is not limited to the activation of spinal cord circuits alone. While sensory structures in the brain such as the thalamus and somatosensory cortex are activated by noxious input, so are areas such as the cingulate cortex (emotion) and prefrontal cortex (cognition). While brain imaging studies specific to chronic postoperative pain are limited in number, many relevant investigations involving neuropathic, musculoskeletal and visceral pain have been completed shedding light on brain changes underlying the acute to chronic transition. These alterations in the brains of patients with chronic pain can be divided into changes in activation state, structure, connectivity and cortical organization [14]. Briefly, some of those changes are:

Activation: In patients with chronic pain, the anterior cingulate and prefrontal cortices, areas involved in the affective component of pain, are differentially regulated.

Structure: Reductions in grey matter have been noted in several imaging studies in involve changes in the anterior cingulate, thalamus, insula and hippocampus.

Connectivity: This parameter reflects the communications between different regions of the brain. One of the more reproducible patterns of change is in the so-called default mode network. This network reflects the coordination of activity between brain centers when a person is not focused on a task.

Cortical organization: Changes in cortical representation and reorganization are especially common after amputation and spinal cord injury, but can occur in other chronic pain syndromes. The degree of reorganization has been correlated with post-injury pain. Likewise, normalization of cortical representation is associated with reduced pain.

Unknown is when and to what degree these changes are reversible and which of the changes explain the various symptoms of pain centralization. Evidence from others investigating brain mechanisms for chronic pain suggest therapies like cognitive behavioral therapy (CBT) [15], ketamine infusion [16], and antidepressants [17] may reverse the pain-related brain changes and associated pain, cognitive and emotional symptoms. CBT has been shown to reduce hyperalgesia in controlled experimental settings as well [18]. When and how specific imaging parameters can be used as biomarkers of specific types of persistent pain remains undefined.

The vulnerable brain

Recognizing the important role for the brain in supporting chronic pain, the concept of individuals having a “vulnerable brain” has emerged. This vulnerability is supported first by induced changes or “priming” of brain areas by stressful environmental conditions and diseases (especially psychological ones). The second component is the intrinsic vulnerability of the brain. Recent prospective work suggests that preexisting factors related to corticolimbic neuroanatomical structure are highly associated with the probability of developing chronic low back pain after an acute episode [19]. Similar studies could be performed in surgical patients aided by the very predictable time and date of injury and ability to study patients preoperatively with the hypothesis that these same corticolimbic neuroanatomical features will predict chronic postoperative pain.

Strategies to prevent chronic pain – Medications

Attempts to reduce the rates of chronic postoperative pain build on earlier efforts to provide preemptive or preventative analgesia in earlier postoperative time frames. There are various rationales for these efforts including, 1) because high levels of perioperative pain are predictive of persistent postoperative pain, measures that aggressively reduce perioperative pain may reduce chronic postoperative pain, and 2) specific medications may target receptors, structures or systems that support chronic pain.

The best studied medications for reducing chronic postoperative pain are gabapentinoid drugs and ketamine (reviewed recently in [20]). Gabapentin and pregabalin bind to the alpha-2-delta subunit of certain calcium ion channels. The overall effect is to reduce the activity of the associated neurons thus reducing some forms of pain, especially neuropathic pain. Many studies are available studying the effects of these drugs on early-term postoperative pain. Those results are somewhat mixed with effects possibly specific to particular types of surgery. Likewise, several trials are available examining longer term pain outcomes using perioperative gabapentin and pregabalin. Systematic review of those data did not provide a clear conclusion as to long-term efficacy. Our knowledge base in this area suffers from lack of consistent dose and duration of treatment using the gabapentinoid drugs.

Ketamine is a drug with multiple targets including the NMDA receptor. This receptor is key in establishing LTP, a process intimately involved with memory and persistent pain after injury. Many studies using ketamine are available, most of which involve protocols with a loading dose followed by infusions terminating at wound closure, PACU discharge or after some time on the postoperative ward. The drug is generally very well tolerated at low doses, and few neuropsychiatric side effects were seen when infusion rates were low. A recent Cochrane Database review suggested that these protocols were in fact effective in reducing chronic postoperative pain. This drug may have special value in the perioperative pain treatment of patients receiving opioids for pain [21].

Strategies to prevent chronic pain – Neural blockade

Strategies involving neural blockade leverage the concept that preventing or reducing the barrage of afferent input might prevent neuroplastic changes in the spinal cord and brain linked to chronic postoperative pain. Techniques included in this group are epidural anesthesia, paravertebral blocks and other more peripheral blocks with or without catheter administration of local anesthetic. One recent Cochrane review found beneficial effects of epidural and paravertebral blocks in thoracotomy and breast surgery patients for 6-12 months [22]. Other studies have shown benefit for regional techniques in terms of reducing persistent pain for various periods for laparotomy, cardiac surgery and others although sample sizes for all these analyses remain fairly small. The duration and density of the blocks necessary to achieve prevention of chronic pain have not been defined and remain important research priorities.

Strategies to prevent chronic pain – Rehabilitative

Complementing pharmacological and interventional strategies for pain management are ones based on behavioral and rehabilitative approaches. “Prehabilitation” is being discussed more often these days as an approach to optimizing physical condition prior to surgery to promote optimal outcomes. While some evidence suggests prehabilitation can reduce acute postoperative pain, little information related to the effects of prehabilitation on long-term pain is available. Recently a hybrid cognitive-behavioral-physical therapy (CBPT) postoperative program was used to optimize the outcome of high risk patients after spine surgery [23]. Both pain and disability were improved in the active program vs. an education only group when treatment was initiated 6 weeks postoperatively. Studies like this demonstrate that even postoperatively it may be possible to target therapies on groups of patients with higher than normal likelihoods of poor pain-related outcomes.

Conclusions

Chronic postoperative pain is remarkably common although it has received very little attention until recently. Beyond pain, these patients tend to experience higher rates of depression, anxiety and cognitive changes. There are likely many etiologies for this type of pain, but pain due to intraoperative nerve injury is one clear cause. Among the changes occurring within the nervous system that support chronic postoperative pain, spinal cord sensitization and neuroplastic changes in the brain are strongly linked to ongoing pain as is deficient descending inhibition. The prevention and treatment of this type of pain are at early stages. The perioperative use of ketamine and gabapentinoid drugs has some support as does the use of regional anesthesia. Amongst the most important unanswered questions for the prevention of centralization and chronification of pain after surgery are, 1) How do we identify those at greatest risk?, 2) How do we help the patient understand this possible complication of surgery?, and 3) What are the best strategies for preventing and treating chronic postoperative pain?

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Anesthetic Neurotoxicity: Should We Be Concerned?

James E. Cottrell, M.D. **Brooklyn, New York**

The assumption that anesthetics and sedatives do not harm the central nervous system is probably true for most patients. However, for patients less than one year old, or more than 65 years old, that assumption is under challenge from a substantial body of evidence. Fetuses and infants appear to be at risk because systems that would enable them to fully recover from the effects of more than 2 hours of anesthesia are still in development. In distinction, seniors may be at risk because systems that once enabled full recovery have ever-diminishing capacity. Even for some patients between the age of 1 and 60 years, full neurologic recovery may require replacing apoptosed neurons and pruning dendritic spines, leaving them not quite the same person that they were prior to surgery.

THE YOUNG BRAIN

After 28 weeks of gestation, fetal neurons develop an acute ability to die from boredom.[1] Given 78-94 billion neurons in the adult human brain,[2] and evidence that at least one proto-neuron, and more likely two, undergo apoptosis for each neuron that survives,[3] a midpoint estimate is that the human brain averages more than 19,000 apoptotic proto-neuron deaths per second during the last 11 weeks *in utero*. Those cellular suicides are selective, leaving the core material and sculpting the primary architecture for subsequent CNS development.[4-6]

The trigger for much of that avalanche of apoptosis is a lack of synaptic feedback. Apoptosis appears to be the default program of many excitable cell types, with cell-typical activity promoting proteins like anti-apoptotic Bcl-2's that prevent the default program from running its course. Put differently, the old saying "Use it or lose it" is not only for the old … synaptic activity may be as crucial to the survival of fetal neurons as are O_2, ATP and CBF. So what happens to fetal and 0-1 year old neurons that would be receiving and sending signals were it not for the presence of anesthesia?

In laboratory animals

One of the first animal models to test the effect of anesthesia on fetuses was developed by Chalon in 1981. He exposed pregnant mice to halothane and found that their offspring, and the offspring of those offspring, learned significantly more slowly than first and second generation controls.[7 see also 8] Analogous findings for offspring exposed *in utero* have been extended to isoflurane,[9,10] sevoflurane[11] and propofol[12] in rodents and to ketamine[13] and isoflurane[14] in fetal rhesus macaques. Takaenoki et al also reported cross-generational effects: neonatal exposure of female mice to sevoflurane causes subsequent deficits in maternal behavior that lead to decreased survival of their non-exposed offspring.[15] That finding comports well with Amrock et al's finding that "even brief exposures [to sevoflurane] induce long-lasting alterations in neuronal circuitry and sensitize surviving synapses to subsequent loss."[16] The possibility of epigenetic effects notwithstanding, early laboratory reports indicating a problem did not receive the attention they deserved until 2003 when Jevtovic-Todorovic and colleagues published "Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits" — a title that says it all.[17] Many subsequent studies have confirmed those findings for neonatal exposure to desflurane, isoflurane, sevoflurane, propofol, nitrous oxide and ketamine in rodents.

Postnatal apoptosis consequent to a clinically relevant depth and duration of general anesthesia also occurs in mammals with periods of rapid synaptogenesis more analogous to humans, including pigs[18,19] and non-human primates.[20-23] Potentially relevant for burn victims, twenty-four hours of "a light surgical plane" of ketamine anesthesia also causes long term cognitive deficits in Rhesus macaque neonates.[24] In addition to apoptosis, Stratmann and colleagues found that exposing 7-day-old rats to four hours of isoflurane induced a decrease in neurogenesis that contributed to a permanent deficit in hippocampal-dependent learning and memory.[25] Using 16-day-old rats, Briner and coauthors found that sevoflurane, desflurane, isoflurane[26 see also 27] and propofol[28] rapidly increase dendritic spine density, which "could interfere with physiologic patterns of synaptogenesis and thus might impair appropriate circuit assembly in the developing cerebral cortex." Jevtovic-Todorovic's group recently found that neonatal propofol exposure changes synaptic plasticity proteins and increases stereotypic and anxyolitic behavior in adulthood,[29] and Huang and Yang have added "reduction in synaptic structural plasticity" as a cause of impaired motor learning during adulthood in mice exposed to ketamine-xylazine 3 times between post-natal days 14-18.[30] Many of these mechanisms probably contribute to Raper and colleagues finding that 4 hours of sevoflurane anesthesia during postnatal day 6 to 10 increases anxiety-related behavior at 6 months of age in Rhesus macaques.[31]

In humans

Levy reported a significant association between near-term emotional sequelae and younger age at anesthetic exposure in 1945 ($p<0.0004$, data not statistically analyzed in the original article).[32] Subsequent reports support an association between impaired neuro-cognitive-behavioral development and exposure to surgery and anesthesia[33-64, 69] with several supporting the relationship between younger age and increased detrimental effects,[e.g. 46, 49] suggesting that the period of extraordinary vulnerability in humans is *in utero* to twelve months postpartum – similar to that found at analogous developmental stages (as distinct from chronological ages) in non-humans.

If duration of general anesthesia is as critical in human fetuses and neonates as it is in nonhuman mammals,[19] then 30-60 minutes of exposure is not sufficient to affect currently measurable long-term learning capacity, even in the high-vulnerability age group. Accordingly, Hansen and colleagues finding of no substantive impairment in children "exposed to a single, brief anesthetic procedure in infancy,"[65] and Davidson et al's

GAS Study finding of no difference between general anesthesia and awake regional anesthesia during infancy for a single, brief exposure,[66] suggest that measurable deleterious effects start taking effect beyond one hour of exposure.[cf. 67] In an effort to partially control for genetic variation, The Pediatric Anesthesia Neuro Development Assessment (PANDA) study compared children exposed to general anesthesia prior to 3 years of age during hernia repair versus siblings of similar age (within 3 years) who were not exposed to general anesthesia prior to age three.[68] Unfortunately, like the Davidson[66] and Hansen studies,[65] this investigation probably tested for an effect of exposures that were too brief to have a measurable effect in a study population that was substantially composed of children who were too old to be sufficiently susceptible – i.e., too little too late. Long-term learning deficits generated by brief exposures notwithstanding, Whitaker and coauthor's recent finding that "A brief (approximately 60 min) exposure to isoflurane general anesthesia, without induced surgical stress, significantly increased serum IL-1ß, a selective activation marker of systemic inflammation" suggests a mechanism for measurable damage from longer exposures.[69] In distinction to a single brief exposure, Wilder et al[44] and Yan et al[54] found that repeated brief exposures to general anesthesia have a measurable deleterious effect on neurodevelopment.

Block and colleagues analyzed achievement test scores of 7-17 year-old children who received general anesthesia for up to 3.75 hours during infancy for procedures that are not associated with cognitive impairment. After excluding children with any of 14 pre-specified CNS problems or medical conditions associated with learning disabilities, they found that a substantial proportion of children without such risk factors scored below the 5th percentile of the normative population ($p<0.01$), with increased duration of anesthesia associating with reduced performance.[49] Bong et al also found increased learning disabilities at age 12 in healthy children exposed to 30-120 minutes of sevoflurane prior age 1.[55] In distinction to Block and Bong's finding for children exposed to general anesthesia, Williams et al did not find a significant difference in the percentage of children scoring below the 5th percentile, nor a correlation between achievement scores and duration of surgery, in children who received spinal anesthesia during infancy.[67]

To date, perhaps the most intriguing evidence for separating surgically and/or genetically induced neurodevelopmental deficits from anesthesia/sedative-induced deficits comes from children anesthetized for craniosynostosis[51] and reconstructive heart surgery,[52,57] or sedated for procedures during neonatal care.[58] Naumann et al found a stronger association between anesthesia duration and neurodevelopmental delays at 36 months of age than between surgical duration and neurodevelopmental delays in children who had non-saggital, single suture craniosynostosis when they were about 6 months old.[51] "After adjustment for multiple relevant covariates" Andropoulos et al found "an association between VAA [volatile anesthetic agents] exposure ... and lower neurodevelopmental outcome" at 12 months of age after complex neonatal cardiac surgery.[52] Diaz and coauthors found a similar result. They performed a retrospective dose-response study on 96 infants who underwent staged reconstructive surgery for hypoplastic left heart syndrome. Initial surgery with cardio-pulmonary bypass was performed at less than two months of age. All subsequent surgical interventions as well as ICU stays, up to neurodevelopment assessment at age 4 years, were included in a cumulative anesthetic exposure analysis. After adjusting for multiple covariates previously demonstrated to influence neurodevelopmental outcomes, they demonstrated that greater exposure to VAA is correlated with lower full-scale IQ.[57] Particularly telling, Duerden et al also found a dose-response curve between midazolam and lower cognitive scores with reduced hippocampal volumes at age 18-19 months in preterm neonates sedated for stressful and painful procedures during neonatal intensive care.[58]

Just as preterm infants appear to be more sensitive to harmful effects of anesthesia and sedation than full-term infants, effects in fetuses may be even stronger than those in post-natal infants. In 1986 Hollenbeck and coauthors reported decreased cognitive capacity in four-year-olds whose mothers had been anesthetized while they were *in utero*.[59] Several subsequent studies found analogous associations between pre-natal exposure to anesthetics and developmental problems including autism,[60] hydrocephalus,[61] diminished general intelligence,[62] impaired spatial ability,[63] small head size and mental retardation.[64]

Upcoming Trial?

At the *SmartTots* Workshop on June 20, 2014, McCann and Davidson put forth the null hypothesis that "Infants who undergo the cleft lip/palate repair with an average of >8 hours of general anesthesia in the first year of life exposed to conventional general anesthesia with sevoflurane and nitrous oxide will have similar neurocognitive outcomes to infants exposed to an 'apoptosis sparing' general anesthetic." The core of their "apoptosis sparing" anesthetic is dexmedetomidine with remifentanil, the efficacy of which is being tested in the "T REX" trial.[70] Presumably, if T REX demonstrates feasibility, a trial comparing dex/remi maintenance to sevo-N2O maintenance on subsequent neurocognitive development will follow. Prospective clinical trials that compare potentially less neurotoxic anesthetic regimens, perhaps dex/remi xenon, to conventional alternatives in children who receive sufficient anesthesia at a young enough age to test the anesthesia-neurodevelopment hypothesis ... children for whom delaying surgery is seldom an option ... will address the most important question: Is there a better way anesthetize children? Such trials are long overdue.

Have the data already changed clinical practice?

How would you answer the following question?

A 27-year-old woman presents with an operable, slow-growing, benign, mildly symptomatic brain tumor. Her neurosurgeon has scheduled the case and estimates an operation time of 4.5 hours. She is 25 weeks pregnant. Would you:

A. Proceed with the case using state-of-the-art equipment, procedures and a volatile anesthetic for maintenance?

B. Discuss evidence that has emerged or gained renewed recognition since 2003 that 4.5 hours of anesthesia may cause neuro-degeneration and persistent learning deficits in the developing brain and leave the decision to the neurosurgeon?

C. Discuss the above evidence with the neurosurgeon and the parents and leave the decision in their hands?

D. Discuss the above evidence with the neurosurgeon and the parents and, barring development of substantive symptoms, advise postponing surgery until after the patient has given birth?

My guess is that prior to Jevtovic-Todorovic and coauthors' 2003 shot-heard-round-the-anesthesia-world,[17] most of us were on the A train. In the absence of survey data, my hope is that most of us would now follow a suggestion from Rappaport et al: "parents and care providers should be made aware of the potential risks that anesthetics pose to the developing brain ... surgeons, anesthesiologist, and parents should consider carefully how urgently surgery is needed"[71] ... and opt for C or D because, as put by Drasner, "If you aren't concerned, you haven't been paying attention."[72 see also 73]

How might we fix this problem?

Olney and his group proposed that anesthetic drug effects on fetal and neonatal gamma-aminobutyric acid and N-methyl-D-aspartic acid receptors cause translocation of pro-apoptotic proteins to mitochondrial membranes, leading to an apoptotic cascade.[74] Perhaps this problem can be alleviated through anesthetic management. Dexmedetomidine has been shown to be non-neurotoxic in a fetal non-human primate model[75] and has been shown to ameliorate the apoptosis caused by ketamine,[76] isoflurane,[77] and propofol[78] in the developing rodent brain.

Several adjunct pharmaceuticals have also shown promise. L-carnitine, an l-lysine derivative that transports long-chain fatty acids into mitochondria, appears to have a beneficial effect in N2O/isoflurane-damaged neonatal rats.[79] Lithium reduces damage from ketamine and propofol in neonatal mice[80] and Brambrink's group found that lithium protects against anesthesia neurotoxicity in the infant primate brain – completely preventing isoflurane-induced neuroapoptosis and significantly reducing apoptosis of oligodendroglia.[81] Clonidine reduces the apoptotic and behavioral effects of ketamine in neonatal mice[82] and Patel's lab has shown that inhibition of p75 neurotrophin receptors attenuates both isoflurane[83,84] and propofol[85] neurotoxicity in mice. Using the early post-natal rat model, Yon and coauthors found that melatonin reduced anesthetic-induced damage in the most vulnerable brain regions: "Melatonin-induced neuroprotection was mediated, at least in part, via inhibition of the mitochondria-dependent apoptotic pathway since melatonin caused an up-regulation of the anti-apoptotic protein, bcl-X_L, reduction in anesthesia-induced cytochrome C release into the cytoplasm and a decrease in anesthesia-induced activation of caspase-3 [precursor of apoptosis]."[86] More recently, Jevtovic-Todorovic's lab found that both EUK-134, a synthetic reactive oxygen species scavenger, and R(+) pramepexole, a synthetic aminobenzothiazol derivative that restores mitochondrial integrity, "completely prevented general anesthesia-induced cognitive impairment" in rats that had been exposed to 6 hours of midazolam/isoflurane/N2O anesthesia on post-natal day 7.[87 see also 88,89]

Erythropoietin (EPO) is another promising adjunct. Pellegrini and colleagues have presented evidence that EPO substantially diminishes neurotoxicity and later learning deficits in rat pups exposed to sevoflurane on post-natal day 7.[90] O'Gorman et al found evidence of improved white matter development at 12-18 and again at 36-42 hours after birth in preterm human infants given recombinant EPO within 3 hours of birth,[91] and the Neonatal Erythropoietin and Therapeutic Hypothermia Outcomes study recently reported that newborns given EPO for hypoxic-ischemic encephalopathy had improved 1-year motor scores,[92] and lower volume of brain injury.[93]

THE OLDER BRAIN

The older brain has less cognitive reserve — less resilience subsequent to neurological challenges. Oxidative phosphorylation does not work as well. We acquire genetic mutations that can alter outcomes. Genetic alleles that were silent when we were young manifest themselves as we age. And then there is free radical build-up with reduced levels of scavengers like vitamin C, melatonin and vitamin E. All of these dreary realities probably contribute to Kline and coauthors' finding that "Elderly subjects after surgery experienced an increased rate of brain atrophy,"[94] and as found by Silbert et al,[95] "subjects with mild cognitive impairment suffered greater subsequent cognitive effects."

POCD After Non-Cardiac Surgery

In 1955 P.D. Bedford published "Adverse cerebral effects of anaesthesia on old people."[96] He reviewed 1,193 (presumably non-cardiac) patients over 50 years old who had received general anesthesia. Mental deterioration in 10% of patients appeared to be long-term or permanent — a figure that concurs with subsequent findings. Bedford concluded that cognitive decline is related to anesthetic agents and hypotension. He recommended that "Operations on elderly people should be confined to unequivocally necessary cases" and that "postoperative medication should not be a routine matter." The next major study to report POCD skips ahead 43 years to 1998 — the first International Study of Postoperative Cognitive Dysfunction (ISPOCD).[97] In non-cardiac patients more than 59 years old, the incidence of cognitive dysfunction 1 week after surgery was 22% higher than in age-matched controls and 7% higher 3 months after surgery ($p<0.004$ for both) with 10% of patients evidencing POCD. So the ISPOCD results were identical to Bedford's finding at a longer postoperative interval. Increasing age, duration of anesthesia, lesser education, a second operation, postoperative infection, and respiratory complications were risk factors for early postoperative cognitive dysfunction. However, under a circumstance of significantly reduced statistical power due to a 22% loss of follow-up at 3 months, among the risk factors that were significant in the early postoperative period, only age remained statistically significant.

Monk and colleagues found that 12.7% of elderly (>59 y o) non-cardiac patients had POCD three months after surgery[98] — again, within a narrow confidence interval around Bedford's 1955 report. Corroborating earlier work,[99] Monk's study also found a substantial relationship between POCD and death within one year of surgery.[see also 100,101] Independent risk factors for sustained POCD included greater age, less education, POCD at hospital discharge and a history of stroke without residual damage. Consistent with many investigations, more education may indicate greater pre-surgical cognitive reserve, just as prior stroke may indicate pre-surgical reduction of cognitive reserve.[101,102] Notably, Monk's '08 study did not find duration of anesthesia to be a risk factor. However, the risk of a false negative conclusion is high in that regard, because the sample size of elderly patients at the 3-month measurement was even smaller (308 with 39 POCD patients[99]) than in the International Study of POCD (901 with 91 POCD patients[97]). The longest follow-up study of POCD patients (median = 8.5 years) was published by the ISPOCD group in 2009: "Cognitive dysfunction after noncardiac surgery was associated with increased mortality, risk of leaving the labor market prematurely, and dependency on social transfer.[103]

POCD After Cardiac Surgery

Most of us have heard friends or relatives say something like "since he had open-heart surgery, he's not the same … he can't think as well, he's not as happy." The *New York Times* brought attention to this problem with an article entitled "Saving the Heart Can Sometimes Mean Losing Your Memory."[104] In that article, Jauhar explained the basics of extracorporeal circulation and discussed reasons for memory loss, focusing on a patient who had gone back to work and found that he had difficulty with his job … a patient who could not perform functions that he had performed for many years. That article raised a great deal of concern, setting the stage for a paper published a year later in the *New England Journal of Medicine* by Newman and colleagues.[105 see also 106] They found POCD in 53% of Coronary Artery Bypass Graft (CABG) patients at discharge and in 36% of patients six weeks later. That proportion went down to 24% six months after surgery, but came back up to 42% five years after surgery — a pattern of early improvement followed by subsequent decline that was predicted by POCD at discharge.[see also 107] Evered et al subsequently found strong associations between POCD at 12 months after CABG surgery and death within 10 years, and dramatically increased incidence of dementia 7.5 years after CABG surgery.[108]

The factors that cause decline in cognitive capacity among non-CABG patients also affect CABG patients. However, some of those risk factors, like duration of exposure to anesthetics, may be masked by damage done to CABG patients from increased liability to cerebral emboli, cerebral ischemia during re-perfusion, and over-warming after bypass.[109]

Aggravating Factors

- On-pump vs. Off-pump

Does on-pump versus off-pump make a neurocognitive difference? Several trials failed to detect a neurocognitive advantage for off-pump patients.[110-112] Although Shroyer et al did not find a statistically significant difference across their composite test battery, they did find a significant difference on one important test in favor of off-pump, suggesting the possibility of a false negative conclusion.[110 cf. 113] Both the 1-year follow-up from the CORONARY investigators[111] and the GOPCABE study group[112] failed to find a statistically significant advantage of off-pump bypass. Statistical significance aside, both investigations found a lower incidence of stroke in off-pump patients and Kowalewski et al's recent meta-analysis of 100 investigations covering 19,192 patients found a 28% reduction in stroke for off-pump bypass ($p<0.009$).[114] So we are left wondering how patients who experience more strokes (on-pump patients) did not evidence statistically significantly worse neurocognitive outcome. One reason is that in the CORONARY study some surgeons took the liberty of performing off-pump surgery on 102 patients who had been randomly assigned to on-pump surgery because those patients had calcification of their aortas. In the intention-to-treat analysis, those patients' results were analyzed as if they had on-pump surgery.[115] These profound protocol violations were accompanied by patient-selected, as distinct from randomly selected, inclusion in neurocognitive testing.[111] Dr. Hartung and I have argued that intention-to-treat analysis should always be accompanied by on-treatment analysis,[116] and calculating a 'p' value for non-random samples makes no sense. In this case "absence of evidence is not evidence of absence,"[117] and unless strokes do not have neuro-cognitive consequences, my best-guess is that the CORONARY study should be disregarded.

Puskas and colleagues found that "After a mean of 7.5 years of follow-up, patients undergoing off-pump coronary artery bypass performed better than those undergoing [on-pump] cardiopulmonary bypass in several neuropsychological domains,"[118] and in what amounts to a serendipitous positive-control study, Li et al found that preconditioning with hyperbaric oxygen reduced markers of cerebral injury in patients undergoing on-pump bypass but not in patients having off-pump bypass, reasoning that "the protective effects of HBO preconditioning may only manifest when there is a relatively severe injury, such as an on-pump procedure and not in off-pump CABG surgery patients."[119] Subsequently, Brewer and coauthors found more postoperative complications, including permanent strokes, in 3,898 on-pump patients who were baseline-matched to 3,898 off-pump patients.[120] More recently, Kok et al's prospective study found substantially less POCD 3 months after CABG surgery in patients randomized to off-pump.[121]

Less direct evidence came from a study of over 16,000 patients in whom a greater incidence of delirium occurred after on-pump cardiopulmonary bypass, with duration of surgery (and so anesthesia) as a significant risk factor.[122] Although these patients were not followed up for POCD, Girard and coauthors found that in "mechanically ventilated medical intensive care unit patients, duration of delirium (which is potentially modifiable) was independently associated with long-term [12 month] cognitive impairment[123] and Morandi et al found that "delirium duration in the intensive care unit was associated with white matter disruption at both discharge and 3 months later with worse cognitive scores up to 12 months after discharge."[124] In a prospective study of 225 CABG patients, Saczynski and and coauthors found that "Delirium is associated with a significant decline in cognitive ability during the first year after cardiac surgery"[125] and in 263 Alzheimer's disease patients, Gross and colleagues concluded that "Delirium is highly prevalent among persons with Alzheimer's disease who are hospitalized and is associated with an increased rate of cognitive deterioration that is maintained for up to 5 years."[126] Neufeld et al found that post-op delirium in the PACU "is associated with subsequent delirium on the ward, and ... with a decline in cognitive function and increased institutionalization at hospital discharge."[127] More recently, Mangusan et al also found that: "Patients with postoperative delirium had significantly longer stays and greater prevalence of falls than did patients without delirium. Patients with delirium also had a significantly greater likelihood for discharge to a nursing facility, greater need for home health services if discharged to home, and a significantly higher need for inpatient physical therapy (all $p < .001$)."[128] Most recently, Royse et al found that patients who experienced delirium after cardiac surgery were less likely to recover cognitive capacity 6 months post-op.[129] Clearly, a relationship between depression, sedation, delirium, poor neurological outcome and POCD should not be discounted,[122-135] such that off-pump patients may be at lesser risk for POCD.

- Inflammation

Inflammation caused by surgical trauma may also aggravate POCD and is associated with the pathogenesis of Alzheimers' Disease (AD) in a mouse model.[136] Evidence that the association is causal comes from Vom Berg and coauthors' finding that intracerebroventricular delivery of anit-p40, and inhibitor of inflammatory signaling, significantly reduces the concentration of amyloid β (Aβ) and reverses cognitive deficits in aged Alzheimer's mice.[137] We know about the up-regulation of IL-1, and this in turn can affect anesthetic receptors.[138] The ensuing cascade of events ultimately affects the anesthetic gamma-aminobutyric acid and N-methyl-D-aspartic acid receptors and increases production of Aβ … and we know that soluble oligomers of Aβ, even in non-demented patients, associate with cognitive problems. Genetic predispositions are another aggravating factor. For example, Matthew and coauthors have shown the contribution of P-selectin and C-reactive protein alleles in modulating susceptibility to cognitive decline caused by inflammation after cardiac surgery,[139] and Cai et al found an association between APOE4 and early POCD in elderly patients undergoing inhalation anesthesia.[140]

- General Anesthetics

Are anesthetics aggravating factors? If so, are some more toxic than others? Xie's group found greater cognitive decline in patients 1 week after surgery who received spinal anesthesia with desflurane versus spinal anesthesia with isoflurane or spinal anesthesia alone.[141, cf. 142] Examining autopsy brain tissue, Crary and coauthors found that PKMzeta, an atypical protein kinase C isoform, accumulates in the neurofibrillary tangles of Alzheimer's patients, but not in control patients.[143] One wonders whether anesthetics might increase this tangling in both AD and non-AD patients. My lab is currently investigating the effect of anesthetics on PKMzeta in the adult mouse hippocampus.[144,145]

- Anesthesia and Neurodegenerative Diseases

Do anesthetics aggravate neurodegenerative diseases? Hydrophobic cavities keep sticky proteins from becoming irreversibly glued together. Unfortunately, molecules of inhalational anesthetics can fill those cavities and reduce the amount of energy required to maintain protein assembly.[146] This anesthesia-facilitated disinhibition of protein binding helps monomers aggregate into oligomers, and if those monomers are Aβ, the resulting oligomerization can lead to protofibrils that are small enough to diffuse into neurons and large enough to be neurotoxic. Soluble Aβ oligomers[147] and alpha-Synuclein[148] appear to contribute to the neurodegeneration characterized by Alzheimer in the early 20th Century. Thirteen million Americans are projected to have AD by the middle of the 21st Century. Many of them will need to be anesthetized, and many of those will have been anesthetized before they became demented.

The role of inhalational anesthetics in the above scenario has been verified *in vitro* by a decade of work from Eckenhoff and coauthors,[149] and is also supported by *in vivo* mouse models.[150,151] In addition to the Aβ-anesthesia connection, Xie's group has utilized human neuroglioma cell cultures to add anesthesia-induced apoptosis as a factor contributing to AD[150, 152,153] and they have found that isoflurane, but not desflurane, degrades mitochondrial function and impairs learning and memory in mice.[154] Do the rodent and cell culture findings apply to humans? Eckenhoff's group reported that the total-tau/Aβ(1-42) ratio in CSF, the only biomarker validated for use in the diagnosis of AD by the Alzheimer's Disease Neuroimaging Initiative (ADNI), elevates during surgery and anesthesia in healthy patients and rises above ADNI's threshold for mild cognitive impairment within 48 hours.[155] In an article entitled "Coronary artery bypass surgery provokes Alzheimer's disease-like changes in the cerebrospinal fluid," Palotas and colleagues found an increased tau/Aβ ratio in patients 6 months after surgery.[156]

Early results from retrospective studies on a possible association between anesthetic exposure and AD were unsettling but inconclusive.[157-159] Now two large studies have found substantial evidence. Matching for age and gender, Pin-Liang Chen and coauthors compared 1,539 patients who had never been anesthetized to 661 patients who had been anesthetized after age 50. Even after adjustment for comorbidities, the patients exposed to anesthesia had a nearly 2-fold greater incidence of dementia ($p<0.001$).[160] Comparing 5,345 patients recently diagnosed with dementia to 21,380 age and gender matched individuals without dementia, Chia-Wen Chen and colleagues found a substantially higher incidence of anesthesia exposure, in a dose-response relationship, among the demented patients ($p<0.0001$).[161] Benzodiazepine use may also be a substantive risk factor, with a "stronger association observed for long term exposures."[162-166 cf. 167, 168] With regard to anesthesia and neurodegenerative diseases, Shoair et al hit the trifecta, finding significant associations between POCD and APOE4 ($p<0.037$), use of highly anticholinergic or sedative-hypnotic drugs at home prior to surgery ($p<0.014$), and anesthesia with sevoflurane ($p<0.01$).[169]

If the association between anesthetic exposure and AD is causal, as evidence indicates for the association between anesthesia and developmental delay in children,[32-64,69] Bedford's admonition from 1953 still holds: "Operations on elderly people should be confined to unequivocally necessary cases"[96] ... and BIS should be kept on the high side, with intravenous anesthesia substituted for inhalational anesthesia when practicable, and with regional anesthesia substituted for general anesthesia when feasible (see below).

Potential Alleviating Factors

- Deeper vs. Lighter & Regional vs. General Anesthesia

Neuman et al found higher mortality and more pulmonary complications in general anesthesia patients compared to regional anesthesia patients undergoing hip fracture surgery,[170] and Brown and colleagues found that elderly patients with serious comorbidities receiving light sedation (BIS>80) during spinal anesthesia for hip surgery had reduced 1-year mortality compared to patients who received deep sedation (BIS≈50).[171] Examining results from 980 patients who underwent intra-arterial therapy for acute ischemic stroke under conscious (light) sedation versus (light) general anesthesia, in addition to finding higher mortality in the general anesthesia patients, Abou-Chebl and coauthors also found poorer neurological outcome.[172] Ancelin found that "Adding sedation to peridural anesthesia led to a decline in verbal secondary memory"[173] and Sieber et al found that lighter sedation during spine surgery led to less delirium.[174] Again, there are empirical and neuropathological reasons to suspect a link between delirium, deep sedation, poor neurological outcome, and POCD.[122-135]

Indeed, presaged by results from a pilot study by Ballard et al,[175] an investigation by the CODA Trial Group of 921 elderly patients undergoing major non-cardiac surgery found that patients with a median BIS of 53 experienced less delirium and had less POCD 3 months after surgery than a control group maintained at a median BIS of 36.[176, see also 177 cf. 178] As put by Green et al, "The important point about this trial is that the investigators were able to maintain an average BIS of 53 in the intervention group vs 36 in the control group. This not only resulted in a significant decrease in POCD but also in postoperative delirium, which we acknowledge is a cause of significant postoperative morbidity ... As our population ages, we can no longer be complacent about how our intraoperative management may affect postoperative outcome."[179]

It may be the case that regional anesthesia with deep sedation is equivalent to general anesthesia when it comes to POCD.[180] Be that as it may, whether the effect is on mortality, morbidity or POCD, a substantial and growing body of evidence indicates that, *ceteris paribus*, lighter is better than deeper and regional is better than general.

- Anesthetics & Sedatives

Are some general anesthetics less deleterious than others? Crosby's group presented data indicating that "In aged rats, propofol anesthesia is devoid of the persistent memory effects observed with other general anesthetic agents in this model. Thus, it appears that general anesthesia-induced memory impairment may be a function of the agent rather than the anesthetic state itself."[181] That surmise is complimented by Ishii et al's recent finding that propofol is associated with less post-op delirium compared to sevoflurane in elderly patients,[182] and Geng et al's finding that propofol associated with less short-term POCD than sevoflurane and isoflurane following laparoscopic cholesystectomy in elderly patients.[183]

Newman's group at Duke reported a significant reduction in POCD at 6 weeks and 1 year among non-diabetic cardiac patients who received i.v. lidocaine. This effect was most pronounced in patients who received less than 43 mg/kg (total dose), while lidocaine appears to have had a deleterious effect in diabetic patients and in patients who received higher total doses.[184] Analysis of a follow-up study is pending.[185] Meanwhile, Chen et al reported that low dose lidocaine reduced early POCD and serum levels of IL-6, TNF-α, S100β and neuron-specific enolase in elderly non-diabetic spine surgery patients.[186]

Dexmedetomidine has been reported to reduce delirium compared to placebo,[187] midazolam or propofol sedation,[188-190] increase survival rate in patients undergoing cardiac surgery,[191] reduce delirium, ventilator time, tachycardia and hypertension compared to midazolam in critically ill ICU patients,[192] reduce focal neurologic dysfunction during mild sedation in patients with supratentorial mass lesions compared to midazolam and propofol,[193] and to reduce early POCD and serum levels of Aβ and Tau protein in orthotopic liver transplant patients.[194]

- Adjuvants, Diet & Exercise

What about erythropoietin, melatonin, vitamin E, memantine, insulin, statins, edaravone and exercise?

Lauretani and colleagues found that EPO levels are lower in 60-to-98-year-olds with impaired peripheral nerve function and/or clinical diagnosis of polyneuropathy.[195] Haljan et al found a trend toward improved neurocognitive recovery with erythropoietin use in CABG patients,[196] and in post-hoc analyses Tseng et all found EPO to be protective in SAH patients who are younger, non-septic, and on statin therapy.[197] More recently, a double-blind trial by Abrishamkar and colleagues found improved Glasgow Outcome Scores in patients with diffuse axonal injury who received subcutaneous injections of EPO every other day for two weeks.[198]

Cheng and colleagues' review of the beneficial effects of melatonin in experimental models of AD is encouraging,[199] as is Ni and coauthors' finding that melatonin premedication attenuates isoflurane-induced Aβ in the hippocampus of aged rats.[200] A clinical trial by Furio et al[201] found that melatonin improved cognitive function in elderly outpatients who suffered from mild cognitive impairment and Wade et al[202] found the same in mild to moderate Alzheimer's patients. More recently, Hatta et al found that a stronger melatonergic sleep agent, ramelteon, prevented delirium in hospitalized older patients.[203]

Several studies indicate that memantine,[204, 205] and insulin therapy,[206, 207] improve cognitive function or delay clinical worsening in AD patients, and vitamin E with other dietary supplements have shown similar promise.[208-210] Perhaps most promising is the human monoclonal antibody aducanumab, which has been shown to reduce brain Aβ and slow decline in AD patients.[211]

The jury has looked hard for evidence that statin therapy prevents or ameliorates AD, but a definitive verdict is still pending.[212] In distinction, Blanco et al found that statin withdrawal increased the incidence of poor outcome in ischemic stroke patients[213] and retrospective reviews by Flint and colleagues found that statin use during ischemic stroke hospitalization[214] and after intracerebral hemorrhage[215] is strongly associated with improved survival and discharge disposition,"[216] even for patients without prior statin use. Tsivogoulis et al found that statin pretreatment in patients diagnosed with acute large artery atherosclerosis associates with neurologic improvement and reduced stroke recurrence.[217] Using a prospective design, Al- Khaled et al found that statin treatment reduced mortality 3 months after acute ischemic stroke,[218] Zhang et al found enhanced recovery with increased brain-derived neurotrophic factor 2 months after ischemic stroke in patients who received atorvastatin[219] and Zheng et al found that adding the free radical scavenger edaravone to atorvastatin increased recovery 2 weeks post-stroke.[220] Pharmacological and mechanical approaches notwithstanding, perhaps age-appropriate exercise remains the best all-round regimen for both prevention and treatment of POCD.[221-230]

- Preconditioning & Perconditioning

Although fetuses and the elderly are particularly sensitive to ischemia, hypo-perfusion and hypoxia, "Nietzsche's Toxicology: whatever doesn't kill you might make you stronger"[231] could lead to improved clinical management of patients with fragile brains.

In 1964 Dahl and Balfour published evidence of "prolonged anoxic survival due to anoxia pre-exposure."[232] This phenomenon was eventually replicated in a model of cerebral ischemia,[233] and induction of endogenous proteins of repair and the genes that code for them are now well documented. Our laboratory has added sevoflurane as a potential preconditioner,[234] and Maze's group reported that in comparison to sevoflurane,[235] nitrous oxide and hypoxia,[236] xenon preconditions in a manner that "might mimic the intrinsic mechanism of ischemic

preconditioning most closely."[235] But if a limited dose of anesthesia triggers the same protective mechanisms as a limited bout of hypoxia, how much anesthesia can we give before what would have been a protective effect becomes a deleterious effect on balance?[180]

Clinically acceptable means of accomplishing cerebral preconditioning are being sought. Volatile anesthetics notwithstanding, pharmacological cerebral preconditioning may be eclipsed by mechanical Remote Ischemic Preconditioning (RIPC). Clinical studies have established that three 5-minute inflations of a blood pressure cuff to 200 mmHg around a patient's upper arm, followed by 5-minute intervals of reperfusion, improves outcome,[237, 238] including near-term POCD,[239] after several cardiovascular procedures and evidence from laboratory investigations indicates that the same technique initiated prior to neurosurgery may improve outcome.[240-243] Investigations of RIPC in neurosurgical patients are underway or have recently been completed,[244] and a study by Hu and colleagues reported reduced biochemical markers of neuronal ischemia and improved rate of recovery after cervical decompression in patients who received RIPC.[245] More recently, Meng and coauthors reported that daily bilateral arm ischemia reduced recurrent stroke and time to recovery over a 300 day period in patients with atherosclerotic intracranial arterial stenosis,[246] and Hougaard et al found that "perconditioning" ischemic stroke patients in the ambulance on their way to thrombolysis therapy reduced tissue risk of infarction at one month post-stroke.[247]

- Neurogenesis

The old adage that neurogenesis is only for the young was shown to be wrong for rodents in 1965,[248] is known to be wrong for non-human primates,[249] and has been reported in humans.[250, 251] This raises the possibility that negative effects of surgery and anesthesia on the elderly, as well as the very young, can be compensated by therapies that strengthen the neurogenic response. Results in rats encourage the conclusion that "neural precursors resident in the brain initiate a compensatory response that results in the production of new neurons. Moreover, administration of growth factors can enhance this compensatory response … [and] we may eventually be able to manipulate these precursors to improve recovery of function."[252, 253] In addition to ischemic preconditioning,[254] granulocyte-colony stimulating factor[255] and erythropoietin[256, 257] appear to be such manipulators, and neurogenesis may be the therapeutic mechanism of electroconvulsive therapy in patients with depression.[258, 259]

CONCLUSION

Reports of possible adverse cognitive effects of anesthetics on young patients appeared in our literature during the 1940's, on elderly patients in the 1950's, and on fetuses in the 1980's ... so these problems and some of their potential solutions are not new, but our awareness of them has experienced a renaissance since 2003.[17] Fortunately, in the vast majority of pediatric cases, anesthesia lasts for less than 1 hour. For that majority, I agree that the "evidence is most consistent with the premise that 'anesthesia per se,' given to an otherwise healthy child who needs only a 'routine' surgical procedure, is not neurotoxic"[260] … or is not toxic enough to cause a currently measurable adverse effect. However, for children less than 12 months old, fetuses of any age and patients over 60 exposed to anesthesia for more than 2 hours, until and unless we are able to classify substantive anesthetic neurotoxicity as a rare complication, the conservative first-do-no-harm approach should: 1) add anesthesia to surgery to the cost side of the cost/benefit equation when making decisions about whether and when to proceed with surgery; 2) avoid nitrous oxide, isoflurane and ketamine in the young because multiple studies indicate that they are particularly toxic; 3) use non-ketamine intravenous anesthesia instead of inhalational anesthesia when doing so is a reasonable option; 4) keep BIS on the high side; 5) limit the duration of continuous anesthesia to less than 2 hours whenever possible; 6) consider the possibility that regional anesthesia with deep sedation may trigger as much neuronal apoptosis as general anesthesia; and 7) when feasible, use regional anesthesia with light or no sedation.

At the very least, newfound concerns generated by available data should inspire a great deal of translational research. If that research is funded, my guess is that we will soon have anesthetic, sedative and adjuvant drugs ranked according to their safety profile … and augmentation of endogenous processes of regeneration will deliver brain protection and recovery to the very young, the old, and everyone in between … before the younger among us are too far gone to benefit!

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ANESTHESIOLOGY 2017
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Perioperative ACLS

Gerald A. Maccioli, MD, MBA, FCCM Plantation, FL

Managing cardiac arrest in the operating room: pre-cardiac arrest considerations, high-stake perioperative cardiac arrest circumstances and therapeutic approaches

Cardiac arrest in the operating room (OR) is potentially a catastrophic event. The magnitude of this event is determined by the nature of the surgical procedure, patient's co-morbidities and the anesthetic used during the procedure. Cardiac arrest during anesthesia and/or the immediate postoperative period is almost always witnessed and often anticipated. Since patients are monitored closely, the event is generally rapidly recognized and treated. Existing guidelines and standard resuscitation methods, including the American Heart Association Cardiac Life Support algorithms, which were developed for use in out-of-hospital and in-hospital cardiac arrest outside of the perioperative space conditions, were not developed with perioperative crises in mind. The development of a protocol-driven approach standardizing treatment algorithms that address the particularities of perioperative cardiac arrest is necessary. The anesthesiologist, as a team leader or a surgical team participant, plays a critical role in optimally managing cardiac arrests. Formulation of an appropriate diagnosis and rapid application of appropriate interventions to treat the underlying cause of cardiac arrest in perioperative settings are essential for optimal patient outcomes. Thus, a working knowledge of procedures to assess and treat cardiac arrest in the perioperative environment is needed for all practicing anesthesiologists. This summary will primarily focus on pre-cardiac arrest considerations as well as on high-stake perioperative cardiac arrest circumstances and therapeutic approaches.

(i) Perioperative cardiac arrest incidence, outcomes and causes:

Perioperative cardiac arrest is a complication that can have disastrous outcomes. Knowledge of the patient, predisposing factors, early detection, aggressive resuscitation and post resuscitation care are the key elements leading to a successful outcome. Analysis of data obtained from 2010 to 2013 from the National Anesthesia Clinical Outcomes Registry, an emerging resource for examination of perioperative and anesthesia-related outcomes, demonstrates that the risk of cardiac arrest was 5.6 per 10,000 cases, which is less than previously reported for in-hospital arrests in surgical patients overall, with an associated mortality of 58.4%.

Patients undergoing emergency surgeries, those having advanced American Society of Anesthesiology (ASA) physical status, and those in extremes of age groups (geriatric, pediatric) have the highest incidence of perioperative cardiac arrest.

Frequent causes of perioperative cardiac arrest that are not explicitly covered in conventional ACLS are: (i) vagal responses to surgical manipulation, vagotonic anesthetics, sympatholysis from anesthetic agents, beta-blockers, and the suppression of cardiac-accelerator fibers arising from T1 to T4 in patients undergoing neuraxial anesthesia; (ii) hypoxia associated with difficult airway management; (iii) pulseless electrical activity (PEA) from hypovolemia; and (iv) circulatory collapse due to auto-positive end-expiratory pressure (auto-PEEP) and inhalational anesthetic overdose. There are also 8 high-stakes perioperative events, namely severe anaphylaxis, tension pneumothorax, local anesthetic systemic toxicity, malignant hyperthermia, severe hyperkalemia, hypertensive crisis, trauma-related cardiac arrest, and pulmonary embolism that may lead to cardiac arrest on the operating table. These perioperative crises, which will be described in the continuation of this summary, are complex, heterogeneous and require rapid implementation of etiology-based resuscitation procedures to prevent mortality from cardiac arrest.

(ii) Pre-cardiac arrest considerations in unstable patients:

To prevent patients from developing cardiac arrest, caregivers must recognize the patient is in crisis. Recognition that a patient is in crisis is more difficult in the perioperative setting because the patient is sedated or under general anesthesia, which precludes adequate monitoring of their mental status or urine production; their respirations are often controlled preventing tachypnea or apnea; surgical positioning often frustrates assessment; and large portions of their body are covered with drapes. Failure to rescue does occur; however, data indicate it is less frequent than suggested.

Considerations for a patient in crisis:

(a) Escalation of care: includes higher levels of monitoring dependent on patient's history, current clinical

status, anesthetic, and procedure. Unstable patients should be monitored with an arterial line and care determined by arterial blood gas evaluations, including base deficit and lactate levels. Insertion of invasive monitors should not delay supportive care or evaluation for a cause of the crisis. Monitoring via central venous access is reasonable and appropriate when central venous oxygen saturations might help guide resuscitation, or when caregivers anticipate infusing vasoconstrictors over longer periods of time. Over the past decade, clinicians have increasingly performed point of care ultrasound to make quick diagnoses and manage a crisis.

(b) Progression to crisis: administration of titrated boluses of vasoactive drugs (i.e. phenylephrine, ephedrine, vasopressin, norepinephrine, and epinephrine) is appropriate and recommended. Small boluses of vasopressin (arginine vasopressin (AVP) 0.5 – 2 u IV) generally will improve hemodynamics when escalating bolus doses of catecholamines have failed.

(c) Left ventricular failure: echocardiography and invasive monitors such as the pulmonary artery catheter guide the management of left ventricular (LV) failure. Hypotensive euvolemic patients with left ventricular shock are managed with inotropic agents in the vast majority of cases. In patients with known, significant diastolic dysfunction, therapy with lusitropic agents such as milrinone will enhance ventricular relaxation and improve cardiac output. Mechanical support with intra-aortic balloon pumps, ventricular assist devices, and extra-corporeal life support (ECLS) (also referred to as extra-corporeal membrane oxygenation (ECMO)) is being increasingly utilized in hospitalized patients with severe LV shock.

(d) Right ventricular failure: similar to left ventricular shock, right ventricular (RV) shock is best guided using a combination of invasive monitors such as the pulmonary artery catheter and/or echocardiography. In most instances, an acute rise in pulmonary vascular resistance (often in the setting of a chronic cause of pulmonary hypertension) causes and sustains RV shock. A combination of inotropes, systemic arterial vasoconstrictors, and pulmonary artery vasodilators such as nitric oxide are used to manage these patients. Patients with right ventricular shock refractory to medical management are increasingly being rescued with mechanical support including ECMO/ECLS and ventricular assist devices when available.

(e) Hypovolemia, and systolic and pulse pressure variation: hypovolemia, a decrease in blood volume, is the most common cause of perioperative hypotension, circulatory crisis, and shock. Pulse pressure variation (PPV), systolic pressure variation (SPV)or stroke volume variation (SVV) are the best indicators of volume responsiveness in hypotensive patients. Measurement of PPV and SPV are most reliable in intubated, mechanically ventilated patients who are synchronous with the ventilator (TV $\geq$ 8 cc/kg). More recent literature suggests that PPV and SPV can be used to assess volume responsiveness in cooperative, spontaneously breathing patients, and are superior to other methods of predicting volume responsiveness in these patients. Obstructive and RV shock cause factitious elevation in SPV and PPV. Hypotension and PPV/SPV values of less than 10% suggest that hypotension and shock will not improve with fluid resuscitation. Although ultrasound assessment of inferior vena cava diameter variation with respiration may predict volume responsiveness, it cannot be easily performed in abdominal, cardiac, and thoracic operations, or in patients in the lateral, prone, or sitting positions.

(f) Ventilation during severe shock or cardiac arrest: Basic Life Support (BLS) guidelines continue to emphasize avoiding hyperventilation during CPR. Patients who are intubated should be ventilated at a rate of 10 breaths·min^{-1} or less, with an inspiratory time of one second. Tidal volume limited to "chest rise" (approximately 500 mL in a 70-kg adult) when the patient is being ventilated with an Ambu bag or similar device. Studies of ventilation during shock repeatedly demonstrate that the duration of increased intrathoracic pressure is proportional to the ventilation rate, tidal volume, and inspiratory time. Because positive pressure ventilation decreases venous return, and hypoventilation seems to cause no harm, patients in shock should be ventilated with lowest settings compatible with a saturation of 90%.

(g) Auto-PEEP: also known as gas trapping or intrinsic PEEP, occurs in patients with obstructive lung

disease. In these patients, mechanical ventilation that does not allow sufficient time for complete exhalation produces a gradual accumulation of air (volume) and an associated increase in pressure (end-expiratory pressure) in the alveoli. This pressure is transmitted to the pulmonary capillaries, and decreases both venous return and cardiac output. The presence of auto-PEEP can be inferred whenever the expiratory flow waveform does not return to the zero baseline in between breaths. Patients at risk for auto-PEEP are best ventilated with the least tidal volume and rate they might tolerate. Generally small tidal volumes (< 6 mL/kg), a low respiratory rate (< 10 /min), and a short inspiratory time [1.2-2 seconds] (which will produce a paradoxical and acceptable increase in the peak inspiratory pressures) will produce the lowest risk of auto-PEEP associated circulatory depression.

(iii) High-stake perioperative cardiac arrest circumstances:

(a) Severe anaphylaxis: When symptoms of severe anaphylaxis are present, moderate doses of epinephrine (100 to 300 mcg) should be given immediately intravenously (IV) to halt mast cell degranulation. Repeated treatment with increasing doses as clinically indicated may be required. If the patient has a pulse, the dose of Epinephrine should not exceed 1 mg. Doses of epinephrine greater than 1 mg IV may be given to pulseless patients. Because laryngeal edema can develop very quickly in these patients, immediate endotracheal intubation is appropriate. Treatment in these patients should include continuous IV infusions of epinephrine (0.05-0.3 mcg/kg/min).

(b) Tension pneumothorax: causes an increase in intrapleural and intrathoracic pressure as a consequence of air that leaks in via a "one-way" valve. This complication is especially concerning in patients receiving positive pressure ventilation in which increased intrapleural pressure throughout the respiratory cycle produces a marked decrease in cardiac venous return, leading to hypotension and PEA cardiac arrest if not recognized in a timely fashion. Patients with tension pneumothorax on positive pressure ventilation develop hypoxemia, tachycardia, hypotension, subcutaneous emphysema, and ipsilateral decreased air entry. Immediate management includes treatment with 100% oxygen and the insertion of a tube thoracostomy by trained personnel or large bore peripheral IV catheter in the mid-clavicular line at the second intercostal space.

(c) Local Anesthetic Systemic Toxicity (LAST): is a life-threatening adverse reaction resulting from local anesthetic reaching significant systemic circulating levels.

Patients with LAST may present with neurologic symptoms including seizures, agitation and obtundation. Cardiovascular complications may include arrhythmia, hypertension, tachycardia and/or progressive hypotension and bradycardia.

The initial treatment of LAST includes insuring adequate oxygenation and ventilation, and using a benzodiazepine to prevent seizures. Early treatment of LAST with infusion of lipid emulsion 20% (ILE) is believed to prevent or mollify cardiovascular complications. If LAST progresses to cardiovascular collapse, high quality CPR will distribute the intralipid throughout the body and may allow ROSC with little or no permanent end-organ damage. Extracorporeal life support should be instituted in cases where there is no ROSC after appropriate therapy and adequate CPR.

(d) Malignant hyperthermia (MH): is a rare life-threatening condition that is triggered by exposure to either a volatile anesthetic agent (halothane, enflurane, isoflurane, desflurane or sevoflurane) or succinylcholine. In susceptible individuals, these drugs induce a drastic and uncontrolled increase in oxidative metabolism in skeletal muscle (hypercatabolic state), The result of this is a dramatic increase in oxygen consumption, CO2 production, and body temperature. These in turn lead to circulatory collapse and death if not immediately treated.

MH is treated with datrolene (2.5 mg/kg intravenously), which has reduced mortality from MH from 80% to 1.4%. Early signs of MH are hypercapnia and sinus tachycardia; additional signs of MH are general muscle rigidity, rising body temperature and tachypnea. MH patient blood gas analyses often show the presence of respiratory and metabolic acidosis. The time to datrolene administration is directly linked to morbidity and mortality from MH, and thus early diagnosis is crucial. If MH is suspected, all volatile anesthesia agents should be immediately discontinued.

(e) Severe hyperkalemia: develops when a serum potassium ≥ 6 mmol/L, and thus this complication is one of the few potentially lethal electrolyte disturbances. Prompt recognition and expeditious treatment of severe hyperkalemia save lives. Severe hyperkalemia is rare, and the most common causes of this complication are renal pathology and drug therapy.

(f) Patients may experience bradycardia and/or bradyarrythmia, hypotension, electrocardiographic changes with peaked T-waves, QRS widening, diminished P waves and a range of arrhythmias including atrio-ventricular blocks, ventricular tachycardia and ventricular fibrillation. Neurological manifestations can include muscular weakness and respiratory failure due to flaccid muscle paralysis.
Treatment with beta-2 agonists (salbuterol) and glucose with insulin can be initiated to promote potassium shift towards the intracellular compartment. If electrocardiographic changes are already present, administration of calcium as a membrane stabilizer is recommended. Treatment with loop diuretics is appropriate in patients that make urine. Renal replacement therapy is often the treatment of choice in patients who make little or no urine. If hyperkalemia is considered reversible, therapy with extracorporeal life support is appropriate.

(g) Hypertensive crisis: is a severe increase in blood pressure that can lead to cardiovascular and neurological complications. Intraoperative hypertension is common and easily treated; however, prolonged hypertension may lead to organ dysfunction and poor outcomes. Morbidities associated with hypertensive crisis include worsening of myocardial ischemia due to myocardial oxygen consumption and left ventricular end diastolic pressure, mitral regurgitation, systolic heart failure, intracranial hypertension, pulmonary edema, acute kidney injury, aortic dissection and bleeding at vascular anastomotic sites. Causes of hypertensive crisis include excessive surgical stimulation, aortic cross clamping, light anesthesia, airway compromise, hypertension due to withdrawal of antihypertensive medications, endobronchial intubation and hypercarbia.

If hypertension is difficult to manage, the differential diagnosis of causes should be expanded to include: pheochromocytoma, hyperthyroidism, malignant hyperthermia, elevated intracranial pressure, carcinoid syndrome, autonomic dysreflexia from spinal cord injury, and increased circulatory volume. Management steps are outlined in Table 1.

(h) Traumatic cardiac arrest (TCA): is potentially catastrophic event that is associated with high mortality. TCA may occur due to loss of blood, severe hypotension, cardiac causes, hypoxia, acidosis, electrolyte disturbance, nerve reflex, drug usage, and anesthesia and/or operation. Treatment of TCA is a team sport, with all measures carried out concurrently rather than sequentially. Success comes from rapid treatment of all potentially reversible pathologies or complications.

If TCA is caused by hypovolemia, the main treatment objective is to achieve immediate hemostasis. It is vastly easier to stop bleeding with pressure than it is to replace the blood that is being lost. Compressible external hemorrhage should be managed with direct or indirect pressure, pressure dressings, tourniquets and topical hemostatic agents. Non-compressible hemorrhage is more difficult; external splints/pressure, blood products, intravenous fluids and tranexamic acid are all used during patient transport and until surgical control has been obtained. At present, the preferred fluid for the resuscitation of a patient with TCA is blood and blood products. A more detailed discussion of the management of traumatic cardiac arrest is beyond the scope of the is summary, and will not be covered in the lecture

Subsequent management of TCA will include damage control resuscitation (DCR), which combines permissive hypotension and hemostatic resuscitation with damage control surgery. Permissive hypotension allows intravenous fluid administration to a volume sufficient to maintain a radial pulse and aiming for a systolic blood pressure of 80-90 mmHg. Hemostatic resuscitation is an early use of blood products to prevent exsanguination, dilution of hemostatic blood components and trauma-induced coagulopathy. Tranexamic acid (TXA) increases survival from traumatic hemorrhage and is incorporated into the protocols for care at most institutions that routinely manage TCA.

(f) Pulmonary embolism (PE): signs of PE under general anesthesia include: (i) unexplained hypotension with concurrent decrease in ETCO2; (ii) desaturation that is only moderately responsive to increased

FIO_2; (iii) transitory bronchospasm with increased airway resistance; (iv) rapid changes of heart rhythm (often dysrhythmias or bradycardia after a transitory tachycardia): (v) unexplained increased of central venous pressure (CVP) or all pulmonary pressures (PAC); and (vi) rapid progression to non-shockable cardiac arrest (usually PEA).

Thromboembolism, venous gas embolism (VGE), and fat embolism are recognized complications that can occur during anesthesia and surgery and are considered the most common cause of pulmonary embolism in periprocedural patients.

Thromboembolism causes circulatory crisis via a combination of mechanical obstruction and the release of inflammatory mediators, which increase the right ventricular (RV) afterload. In severe cases, the associated increase in pulmonary vascular resistance is so great that the right ventricle is unable to maintain the cardiac output. As the RV fails, it typically dilates, and the interventricular septum flattens and shifts toward the left ventricle.

Acute thromboembolism causes cardiac arrest in app. 5% of cases. Echocardiography of the patient with right ventricular shock will typically reveal right ventricular dilatation and dysfunction, with an under filled left ventricle. The management of intraoperative or perioperative thromboembolism is

highly dependent upon the procedure and patient. Therapeutic options range from supportive measures to anticoagulation to thrombolysis.

Like thromboembolism, gas embolism is an important cause of circulatory complication. Patients experiencing gas embolism are breathlessness, develop continuous cough and arrhythmias, myocardial ischemia, acute hypotension with loss of end-tidal carbon dioxide, and cardiac arrest. The risk for a venous air embolism increases when the surgical field is above the right atrium, and thus the focus of hemodynamic support is on improving RV function.

Common causes of gas embolism include laparoscopy, endobronchial laser procedures, central venous catheterization or catheter removal, hysteroscopy, pressurized wound irrigation, prone spinal surgery, posterior fossa surgery in the sitting position, and endoscopic retrograde cholangiopancreatography.

Surgical procedures at risk of VGE should be specifically monitored. Right parasternal precordial Doppler (PPD) ultrasound has very high sensitivity (88%) for air embolism. Trans-esophageal echocardiography allows for recognition of air embolism size and assessment of ventricular function. Patients who survive an embolic event are likely to require continued evaluation and management in an intensive care unit. Management steps are outlined in Table 1.

Table 1: Management of high-stake perioperative events that may lead to cardiac arrest in OR

	Severe Anaphylaxis	Pneumothorax	LAST	Malignant Hyperthermia	Severe Hyperkalemia	Hypertensive Crisis	Pulmonary Embolism
Initial Management	**Pre-arrest:** Stop/remove the inciting agent or drug; stop procedure if possible; arterial blood pressure monitoring; oxygen at FIO2 of 1.0; intubate ASAP for respiratory distress; epinephrine 100-300 mcg in escalating doses ± vasopressin 2U IV; H1 blocker (diphenhydramine 50 mg IV); H2 blocker (famotidine 20 mg IV) ± corticosteroid (50-150 mg hydrocortisone IV or methylprednisolone 1-2 mg/kg IV).	**Unstable patient:** Needle thoracostomy.	**Pre-arrest:** Cease administration of local anesthetic; immediate tracheal intubation with 100 oxygen; transcutaneous or intravenous pacemakers for all symptomatic bradycardic rhythms with pulse; 20% lipid emulsion 1.5 mL/kg IV load, then 0.25 mL/kg/min (~20 mL/min); seizures treated with benzodiazepines.	Discontinue volatile anesthetics and switch from the anesthesia ventilator to manual Ambu bag ventilation from a separate source of oxygen; continue $ETCO_2$ monitoring; stop procedure if feasible; consider switching to IV anesthetic; sodium dantrolene: give 2.5 mg kg-1 or 1 mg lb-1 initial dose and repeat bolus of sodium dantrolene; start active cooling with ice packs and stop it at 38°C;	**Cardiac protection:** calcium chloride or calcium gluconate 1 to 2 gr IV and repeat as required for EKG signs of hyperkalemia. **Drive potassium into intracellular space:** 1 ampule of D50 and 10 units of insulin IV; 50 meq of sodium bicarbonate; albuterol 4-10 puffs.	Deepen anesthetic and administer antihypertensive medications if necessary; place patient in reverse Trendelenberg position; stop surgery if appropriate.	**Pre-arrest:** stop the infusion of the gas or ask the surgeon to flood the surgical field; administer 100% oxygen and intubate for significant respiratory distress or refractory hypoxemia; place patient in Trendelenburg position and rotate toward the left lateral decubitus position; maintain BP with fluid resuscitation and vasopressors/beta-adrenergic agents if necessary.
	Cardiac arrest: CPR if no carotid pulse detected for 10 sec; epinephrine 100-1000 mcg IV, can repeat every 3-5 min or replace with one dose vasopressin 40U IV; if auto-PEEP suspected, disconnect the ventilator briefly and administer adjunctive therapies listed in pre-arrest (H1 and H2 blockers± corticosteroids); extra-corporeal life support in patients getting good CPR.	**Stable patient:** Tube thoracostomy.	**Cardiac arrest:** CPR for prolonged period (at least 60 minutes); if local anesthetic toxicity suspected, epinephrine 10-100 mcg IV is preferable; sodium bicarbonate to maintain a pH >7.25 in patients; therapy with H1 and H2 blockers; aminodarone for ventricular arrhythmias; extra-corporeal life support appropriate if the diagnosis is certain.	remain observant for hyperkalemia, metabolic acidosis, respiratory acidosis, myoglobinuria with oliguria and dysrhythmias; invasive pressure monitoring when feasible; supportive measures for disseminated intravascular coagulation.	**Eliminate potassium or increase corporeal capacity:** 20-40 mg furosemide IV, increase to 1 to 1.5 mg/kg if oliguric response; 30 or 60 g kayexelate OG/NG/PR; induce renal replacement therapy by transfusing washed pRBC (hypokalemic and will absorb serum potassium); in patients with hyperkalemic cardiac arrest, extra-corporeal life support.		**Cardiac arrest:** Circulatory collapse addressed with CPR, and consideration of CPB/emergent thrombectomy if available
Subsequent Management	Determine blood tryptase levels; monitor in ICU for at least 24 hours to avoid recurrence.	Definitive management with tube thoracostomy; If pneumothorax due to lung injury, thoracic surgery.	Monitor for recurrence or delayed progression.	Monitor for 72 hours and treat/cool as required; consider caffeine-halothane muscle biopsy post-crisis.	Monitor serum potassium serially, continue to treat cause(s) of hyperkalemia.	Monitor for recurrence; circulatory collapse should be addressed with CPR.	Consider the right ventricular shock algorithm.

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Occupational Infections: Risks for the Anesthesiologist

Dr. Keith Candiotti

Professor of Anesthesiology and Internal Medicine

Department of Anesthesiology, Perioperative Medicine and Pain Management
University of Miami, Miller School of Medicine
Miami, Florida
USA

OBJECTIVES:

1) Educate Anesthesiologists about the risks that infectious diseases present to them.
2) Review emerging diseases with an emphasis on those transmitted via the respiratory route.
3) Discuss other potentially transmissible diseases such as HIV and Hepatitis.
4) Learn about protective gear and how it should be used and to reduce the risk of transmission.

INTRODUCTION:

The major goal of healthcare personnel (HCP) is to provide for the sick and injured. While caring for the sick, HCP can encounter considerable risk. A large danger to HCPs is their lack of awareness of infection risks and how to minimize them. The intent of this refresher course module is to consider some of the potential occupational risks to HCP, specifically anesthesiologists, as presented by infectious diseases, with an emphasis on emerging infectious respiratory agents as well as those transmitted by contact and blood.

HCP are at increased risk of contracting infections from patients, especially those with emerging diseases that are often not recognized early in the course of an outbreak.[1] There are numerous reports of HCP contracting diseases while caring for patients (e.g. TB, SARS, MERS-CoV). Although HCP are aware of infection control measures, they often show a low level of compliance even in potentially dangerous environments.[2] Additionally, it has been noted that HCP become less compliant with protective measures under stressful situations, such as when they work longer hours.[3]

Each disease outbreak has specific characteristics, and the severity of an outbreak and the risk of infection to the HCP is different in each case, often depending on the agent's characteristics and its mode of transmission.[4] (Fig. 1) The pattern by which infectious agents are transmitted can vary, and a particular disease is often transmitted by more than one route. Transmission routes can be broadly divided into 2 categories, direct and indirect. The direct route occurs when an infectious agent is contracted from the carrier source, such as the patient or a body fluid (i.e. droplet transmission). The indirect route occurs when an infectious agent is contracted via an intermediate, like a doorknob or medical instrument or even from the air. The distinction between droplet and airborne transmission is primarily one of range and timing. Droplet spread refers to relatively large, short-range aerosols that are produced by sneezing, coughing, or even talking. Droplet spread should be considered a direct form of transmission since the droplets can be encountered within a few feet from the patient before they fall to the ground (e.g. pertussis & meningococcus).

Indirect transmission of an infectious agent refers to its transfer from a reservoir to the host by a number of methods including, suspended air particles, inanimate objects (vehicles), or animate intermediaries (vectors). Airborne transmission takes place when infectious agents are carried by droplet nuclei suspended in air or by dust. Airborne dust can include material that has settled on surfaces and then becomes suspended by air currents. Airborne dust can also contain infectious particles blown from the soil by the wind. Droplet nuclei are dried residue of less than 5 microns in size. In contrast to droplets that fall to the ground within a few feet, droplet nuclei may remain suspended in the air

for much longer periods of time and as a result, may be blown over great distances.[5] Measles, for example, has occurred in children who enter a physician's office hours after a child with measles had previously been there. The measles virus is capable of staying in the air for hours.[6]

INFECTIOUS AGENTS:

TUBERCULOSIS:

Tuberculosis (TB) is a leading infectious killer in the world. Approximately, 1/3 of the world's population has contracted latent TB (LTBI), which means that people have been exposed and infected by the TB bacteria but are not currently ill with the disease and cannot transmit the disease. TB may activate in these patients at a later time and it is believed that 80% of active TB cases come from people who were in a latent stage.[13B] In 2015, 10.4 million people worldwide became ill with TB and 1.8 million died from the disease. Over 95% of TB deaths occur in low and middle-income countries. Nearly half of all Global TB cases are reported in just 3 countries, India, Indonesia and China.[6B] In the mid-1980s, a resurgence of outbreaks of TB in the U.S. brought renewed attention to the disease. A total of 9,287 TB cases (a rate of 2.9 cases per 100,000 persons) were reported in the United States in 2016, representing a slight decrease over the prior reported year. Four states, California, Florida, New York and Texas report >500 cases each in 2016, accounting for 50.9% of the cases in the U.S.[7]

HCP are 3 times as likely to contract TB when compared to the general population.[8] The annual risk of latent TB infection in HCP, in low-incidence countries such as the U.S. and Canada, has been reported to be around 2.9%. Of those cases, 49% appear to have been contracted in the workplace. The median estimated annual incidence of TB among HCP was 67 cases/100,000 persons.[8]

Multidrug-resistant TB (MDR-TB) does not respond to isoniazid and rifampin and has become a worldwide health issue. Globally in 2015, an estimated 480,000 people developed MDR-TB, which by definition requires second line drugs (SLD) and treatment for up to 2 years. [7] The mortality from MDR-TB is around 8-21%. Extensively drug-resistant TB (XDR-TB) is a form of multi-drug resistant tuberculosis that responds to an even lower number of available medicines, including the most effective second-line anti-TB drugs. XDR-TB is resistant to isoniazid, rifampicin, quinolones, and at least 1 of 3 injectable SLDs (i.e., kanamycin, capreomycin, or amikacin).[9] It is estimated that about 9.7% of MDR-TB cases are XDR-TB. Increases in the rates of MDR-TB and XDR-TB have been noted in Eastern Europe, Asia and Southern Africa. In the United States, 63 cases of XDR-TB were reported between 1993 and 2011. Some TB control programs have shown that it is possible to cure an estimated 30% to 50% of patients with

XDR-TB.[10] Worldwide, about 52% of MDR-TB patients and 28% of XDR-TB patients are treated successfully overall.[12B] There is no proven preventive therapy for MDR-TB or XDR-TB at this time.[11] Tragically, up to 33% of HCP who contract MDR-TB die.[12] New agents have been introduced to help fight MDR/XDR-TB, bedquiline and delamanid.[12B] Finally, as if MDR and XDR-TB weren't dangerous enough, strains of TB have also been identified in patients for which there are no viable treatment options, appropriately named totally drug-resistant tuberculosis (TDR-TB).[13]

Post-exposure Treatment: If a HCP is exposed to active TB, even if they have had the bacille Calmette-Guerin (BCG) vaccination, they should undergo testing. A tuberculin test (this may be avoided in those people who have had BCG) or interferon gamma release assay (IGRA), whichever is appropriate, should be performed at baseline and again 8-12 weeks post-exposure. Some experts advocate a baseline chest x-ray. If the tuberculin skin test converts to ≥ 5 mm or the IGRA is positive, the individual exposed should be treated with isoniazid and vitamin B6 for 6-9 months. [1] Other protocols are also recommended including use of insoniazid with rifapentine or rifampicin for shorter periods of time. [13B]

Treatment of active disease: First-line treatment is with 4 drugs, isoniazid, rifampicin, pyrazinamide and ethambutol (HRZE) for 2 months, followed by 4 months of isoniazid and rifampicin (HR).[13B]

SEVERE ACUTE RESPIRATORY VIRUS (SARS):

Severe acute respiratory virus (SARS) is a novel coronavirus first reported in Guangdong Province, China in 2002. The disease had a rapid course, spreading to many countries with transmission being demonstrated in 8 countries. Between November 2002 and December 2003, there were 8096 infections and 774 deaths[14] (Case fatality rate [CFR] 9.6%). A high number of HCP were infected during the SARS outbreak.[15] About 20% of cases were reported in HCP. The disease was highly contagious and was transmitted via respiratory droplets and other secretions. It is considered the first global occupational disease of the millennium. The last known case of SARS occurred in 2004.

By the end of the outbreak, 1706 HCP cases were reported to the World Health Organization (WHO). The risk of infection was primarily related to the performance of airway and respiratory related procedures, insufficient or inappropriate personal protective equipment (PPE), reuse of N95 respirators, fatigue and lack of infection control training.[16] In Hong Kong, SARS HCP who wore N95 respirators or medical masks had lower infection rates.[17] The

strongest predictor of SARS transmission from a patient to a HCP was aerosolization of secretions immediately before and during intubation. [15] Another important risk to HCPs was the occurrence of "super-spreaders". These were patients with SARS who transmitted to a large number of contacts and had a higher attack rate.[18,19] Two patients thought to have congestive heart failure and not isolated for 12 hours, led to 10 documented infections (5 in HCP) out of 100 contacts. [15]

SARS transmission to HCP has been demonstrated via: Non-invasive positive pressure ventilation (NPPV), CPR, mask ventilation, bronchoscopy, suctioning, and intubation (the most significant risk factor). As an estimate, any high-risk procedure increases the risk to healthcare personnel by a factor of 3.[20] HCP exposed should be monitored for 14 days after significant exposure.

Post-exposure Treatment: No known vaccine or specific antiviral exist. Treatment is supportive. [4]

MIDDLE EAST RESPIRATORY SYNDROME CORONAVIRUS (MERS-CoV):

The Middle East Respiratory Syndrome Coronavirus is a novel betacoronavirus that can cause a wide spectrum of illnesses from respiratory distress to death. It was first isolated in September 2012, in a patient with fatal pneumonia in Saudi Arabia. The earliest human cases occurred in March 2012, in a group of severely ill HCP in Jordan.[21] Since September 2012, WHO has been notified of 2,066 laboratory-confirmed cases of infection with MERS-CoV and 720 deaths (CFR 35%) in 27 countries. Bats and camels appear to be the natural reservoirs.[22,23] At least 4 large outbreaks of MERS-CoV in HCPs have been reported, all in Jordan. More than 50% of the affected HCP were nurses.[24] Two unlinked cases of MERS have been detected in the US in HCPs who had previously worked in Saudi Arabia. Both were hospitalized and discharged. In the most recent outbreak in Saudi Arabia, July 4-August 12 2017, there 26 cases, with 13 in one hospital cluster. Of the 13, 8 were hospital HCP, they remain asymptomatic. [24B]

Depending on the outbreak, 1-27% of HCP diagnosed with MERS-CoV developed it nosocomially. Risk factors for contracting MERS-CoV by HCPs appears to be, close patient contact and use of a mask rather than an N95 respirator (which showed a higher level of protection).[24C.] Higher transmission rates were felt to be generally due to poor infection control measures. [4] Worldwide cases have been reported after patients were initially exposed in the Middle East.[25] MERS-CoV can remain viable for up to 48 hours on surfaces under hospital conditions. Spread by fecal-oral route as well as respiratory seems probable.[26] In sputum and stool, MERS-CoV can be viable for 16 days and 13 days

in urine. [23] HCP who were exposed to MERS-CoV should be monitored for 14 days for symptoms.**Error! Bookmark not defined.**

Post-exposure Treatment: No known vaccine or specific antiviral exist. Treatment is supportive.

INFLUENZA:

Influenza pandemics have historically occurred several times over the course of each century.[27] In the 1918 influenza pandemic (Pandemic Severity Index [PSI 5] and Case Fatality Ratio [CFR] 2%) 500 million people were infected (1/3 of the world), and 50-100 million died. In 2009, H1N1, in the US alone, produced 57 million cases, with 257,000 hospitalized and 11,700 deaths (CFR 0.02%). In seasonal influenza, the very old and very young are typically affected. In the 1918 and 2009 pandemic, it was mostly children and young adults. [27] In seasonal flu, nosocomial influenza transmission can reach 11-59%.

Influenza (N1H1) 2009: N1H1, influenza was first detected in the US in April of 2009. The index case was a 10-year-old child in California.[28] It was a novel agent, never seen before. It was resistant to the antiviral drugs, amantadine, and rimantadine, but was susceptible to the antivirals oseltamivir and zanamivir. [27] One study demonstrated an infection rate of 65% in ER staff and 35% in OR personnel, compared to a background rate of 13%.[29] It is spread by smaller particles, human-to-human. When its course was finished, 43-89 million people were infected (deaths 8,870-18,300). [27]

Avian Influenza (AI): Avian influenza is common in poultry and is caused by an RNA virus in the orthomyxoviridae family. The first avian A (H5N1) outbreak occurred in Hong Kong in 1997. This variety is highly pathogenic and caused extensive damage to local poultry populations.[30] As of July 25th, 2017, 859 human cases have been reported with 453 deaths (53% mortality) in 16 countries. Four recent cases were in reported in Egypt. In March 2013, another novel avian influenza A was described in China (H7N9). No Transmission cases have been reported outside of China.[29] As of 2017, 1,557 laboratory-confirmed human infections by H7N9 have been reported in China. The case fatality rate is around 40%.[30B] The H7N9 strain continues to evolve and appears to have become more pathogenic. While the overall risk to most humans is low this virus has the potential to continue to mutate in a form that is considered to

have a high potential for pandemic spread.[30C] In most human cases of H5N1 and H7N9 flu, direct poultry or poultry market exposure have been reported.[31] Rare human-to-human transmission of H5N1 has occurred via intimate contact in households where no barrier precautions were used. Transmission has not occurred from casual, social contact.[30] There have been no reports of AI transmissions to HCP. One study demonstrated no transmission to 25 HCP exposed to a patient with H5N1 in a tertiary hospital in Thailand.[32]

AI is widespread in poultry throughout the world. The risk of genetic reassortment and pandemic potential must always be considered and is monitored by the CDC and WHO. This is especially important due to the high mortality noted (>50%). The key to preventing its spread and a pandemic outbreak is early identification of human-to-human contact and adhering to strict infection control practices. (Contact/droplet precautions) [30]

Pre-exposure/Post-exposure Treatment: In November 2013, an H5N1 AI monovalent, adjuvant vaccine for the prevention of AI, was approved by the FDA. The CDC has also begun new trials for a H7N9 vaccine, partially due to the notable increase in cases seen in China and an increased resistance being noted to a prior experimental vaccine developed from the 2013 strains.[30C] To date, testing has demonstrated that H7N9 viruses are sensitive to the anti-influenza drugs in the class of neuraminidase inhibitors (oseltamivir and zanamivir) but are resistant to the adamantanes (amantadine and rimantadine). It has been noted that the newer H7N9 strain appears to be developing resistance to neuraminidase inhibitors.[30C] Current reports from China suggests that when oseltamivir was given early in the course of illness, it demonstrated some efficacy against the H7N9 virus, reducing the severe of illness and death. HCP exposed should be monitored and excluded from work for 7 days (H5N1) and 10 days (H7N9).[33] The seasonal influenza vaccine should be given to all healthcare providers who come into contact with patients. While there is some controversy over this idea overall, it does appear to be beneficial. This year the seasonal flu vaccine covers at least 3 and possibly 4 strains of virus. (The nasal vaccine is not being recommended due to concerns of efficacy). This year's vaccines include coverage for strains of H3N2, currently having some limited spread in China and Asia. Additionally, for providers and patients over the age of 65, an adjuvant (MF59) contained in the vaccine is being offered to help boost the immune response.[33B]

OTHER EMERGING VIRUSES:

Ebola: The first outbreak of Ebola occurred in 1976 in Nzara, Sudan, and Yambuku, Congo (Zaire). In December 2013, the Zaire strain appeared in a small village in Guinea, West Africa but was not identified until March 2014. It

spread rapidly, and as of May 5, 2016, a total of 28,616 Ebola cases have been reported in Guinea, Liberia and Sierra Leone, with 11,310 deaths. Hospitalized fatalities were 31-66%. A total of 852 HCP (Nurses 35% and Physicians 15%) were reported to WHO with 492 deaths (range 44-73%). Transmission occurred via infected body fluids. The incubation period for Ebola appears to be 8-10 days (range 2-21 days).[34]

The Lagos, Nigeria index case was a symptomatic air traveler whose sister died from Ebola. The patient went to the hospital and told them she had malaria. No protective measures were taken. 9 HCP became infected, and 4 died. In the US there were 4 cases. The US index case was from Liberia and came to a Dallas hospital and was discharged home with presumed sinusitis. He later returned sicker and died. 2 nurses test positive for Ebola as a result of caring for the index case. [33]

In a post-acute state, some Ebola patients have demonstrated viral reservoirs in their eyes and/or testicles. Dr. Ian Crozier thought he had recovered from an Ebola infection but developed intense eye pain with reduced vision loss. He also noted that his eye had changed color. Eventually, after treatment, his symptoms and vision improved and remarkably his eye color returned to its original color. He still suffers from other post-Ebola symptoms, joint pain, fatigue, etc.[35]

In any situation where a novel and dangerous agent is suspected, (this is usually the problem early on) protective gear is essential. Gear consisting of a high protection respirator (N-95, N-100 or PAPR), eye goggles, gowns, shoe covers, and gloves are mandatory when an aerosol generating procedure may be performed. Confirmed or suspected cases require airborne isolation rooms (6-12 air changes per hour), especially for procedures. To minimize exposure, as few HCP should be in the room during aerosol-generating procedures as possible. Close contact is considered a minimum of 6-10 ft. from the patient or their room. In outbreaks involving a very infectious or lethal agent, the use of isolation wards should be considered. These wards can often benefit from having separate entrances and exits. To help prevent self-contamination while doffing gear (greatest risk) or donning gear incorrectly, observers should be utilized at the entrances and exits of these areas.[36]

BLOOD BORN AGENTS:

Every year, 600,000-800,000 sharps injuries occur in U.S. healthcare workers.[37,38]

Hepatitis B: A survey of 2400 unvaccinated anesthesiologists in several countries showed a mean prevalence of HBV serologic marker of 17.8% (3.2-48.6%).[39] Hepatitis B (HBV) risk from a percutaneous injury in a HCP with no immunity is 1% to 30%. All HCP should be vaccinated for HBV with demonstrated titers. HBV Post-exposure Prophylaxis (PEP) should be initiated immediately when needed (24 hours is ideal but within 7 days).

Post-exposure Treatment:

HBsAg-Positive Exposure Source: People who have clear documentation that they have completed a hepatitis B vaccine series but did not receive postvaccination testing should be given a single vaccine booster dose. People who are in the process of being vaccinated but who have not yet completed the vaccine series should receive a dose of hepatitis B immune globulin (HBIG) and must complete the vaccine series. Persons who are unvaccinated should receive both HBIG and hepatitis B vaccine as soon as possible after exposure (preferably within 24 hours). The hepatitis B vaccine may be administered simultaneously with HBIG in a separate injection site. The hepatitis B vaccine series should be completed in accordance with the age-appropriate vaccine dose and schedule.[40] (Fig. 2)

Exposure Source with Unknown HBsAg Status: Persons with clear documentation of a completed hepatitis B vaccine series should require no further treatment after exposure relative to HBV. Persons who have not completed the vaccine series should complete it. Unvaccinated persons should receive the hepatitis B vaccine series with the first dose administered as soon as possible. The vaccine series should then be completed. [39]

Hepatitis C: HCV affects 185 million people worldwide and approximately 4 million Americans. More deaths occur each year from HCV than HIV. [40] The rate of HCV, in Anesthesiologists is about the same as the general population, indicating a low transmission risk, although cases have been reported. [38] If the source patient has active HCV the risk is approximately 1.8% (0-7%) from a percutaneous injury. HCV can remain active on a surface for up to 16 hours. Hepatitis D-E infections have also been reported.[41]

Postexposure Treatment: There is no current post-exposure prophylaxis for HCV recommended. Viral testing for HCV RNA at 6 weeks, before HCV-Ab seroconversion takes place, allows for early identification of infection and allows subsequent referral for early evaluation and possible HCV treatment. HCV infection will spontaneously clear

in about 25% of healthy people. Early diagnosis and treatment can increase the rate of HCV clearance to 90% or greater. HCV antibody testing should be performed at 4-6 months after initial testing to rule out HCV infection.[42] (Fig. 3)

Human Immunodeficiency Virus (HIV): In the U.S., there were 58 confirmed cases of HCP occupational conversion (documented negative prior to conversion) as of 2013. In addition, there were 150 possible HCP conversions (no documented negative test prior to testing positive). Actions associate with confirmed conversion (of the 58): percutaneous puncture or cut (49); mucocutaneous (5); both percutaneous and mucocutaneous (2); and unknown (2). Professions at risk (in descending order): Nurse, Laboratory Technician, Physician (nonsurgical), Housekeeper, and Surgery Technician.[43] Only one confirmed HCP conversion has occurred since 1999. In 2008, a laboratory technician injured himself with a needle while handling a live HIV culture. [43,44] HIV transmission rate is 0.3% for percutaneous injury and 0.09% after mucous membrane exposure. The risk of non-intact skin exposure is not known but seems to be less than mucous membrane exposure. [42,43] An older study of Anesthesiologists, Greene et al., estimated a 0.05% conversion rate for HIV percutaneous injury. [43] There is an increased risk of conversion with the following: larger quantity of agent, prolonged exposure, exposed to a patient with a high viral load or advanced disease, deep percutaneous injury, instances where the sharp was in the vein or artery of the infected patient, injury with a hollow bore, blood-filled needle and, limited or delayed post-exposure prophylaxis.

Post-exposure Treatment: PEP should be started as quickly as possible (this requires availability of initial medications that can be accessed 24/7/365 e.g. OR drug dispensing units). The exact time frame is unknown, however, PEP efficacy is believed to decrease with time. HIV PEP should be given for 28 days. If the source status is unclear, then PEP should be started and reevaluated later for continuation. The preferred regimen is raltegravir (400 mg bid) + tenofovir (300 mg) and emtricitabine (200 mg) (Truvada is a fixed-dose combination), which is well-tolerated with minimal drug-drug interactions. This can be used in pregnant women as well (this recommendation is based on limited data). If the source proves to be HIV negative, then PEP can be stopped. In the presence of drug resistance, expert consultation is recommended, however, standard prophylaxis should be started immediately.[45] (Fig. 4)

GENERAL POSTEXPOSURE PROPHYLAXIS (PEP):

After a percutaneous injury with a sharp or needle, wash the area with soap and water to clean the wound. There is no evidence that using antiseptics or disinfectants is beneficial in preventing infection. Bleach should be avoided.[46] After mucosal exposure to blood or body fluids, irrigate the exposed area with water or normal saline.[47] Usually, PEP is best if given quickly. In some diseases, PEP may be effective even if given long after exposure (rabies and tetanus). [46] Live vaccines should not be used in pregnant women or immunocompromised patients. In these groups, immune globulin is preferred. [45] HCP exposed to an infectious agent should be assessed at baseline and at later intervals while at risk. If exposed to blood also test for HIV, HBV, and HCV. [46]

PROTECTIVE MEASURES:

Personal Protective Equipment (PPE): PPE is the last line of defense. Ideally, sick and infectious patients should be identified and isolated in advance. While wearing protective gear clearly reduces exposure risk, the removal of gear presents its own issues. In one study of simulated exposure, 46% of participants contaminated themselves during the doffing procedure. Contamination occurred more frequently with the removal of gloves rather than gowns (52.9% vs. 37.8%, P=.002). Observation helped in reducing contamination (70.3% vs. 30%, P<.001). Training was able to reduce the rate of self-contamination to around 18.9%. Training in advance of an event would seem advisable.[48]

Gloves: FDA has *lowered* the acceptable defect rate for patient exam medical gloves and surgeons' gloves to 2.5% and 1.5%, respectively (Biogels have holes at half this rate 0.65%). Hot, sweaty hands are enough to eat through latex in about 50 minutes (such that HBV and HIV can penetrate). Changing latex gloves approximately every 30 minutes would seem advisable. Therefore, in an 8-hour shift, at least 32 gloves will be used and—at a 2.5% defect rate—statistically, 1 of the gloves will be defective.[49]

Vinyl is the least expensive material however, it is more likely to leak and allow penetration of organisms relative to nitrile and latex. Latex and vinyl are less resistant to perforation than nitrile, but when nitrile does perforate, the holes enlarge faster. [49] In spite of a clear awareness of the risks, and implementation by the CDC of "standard precautions", many HCP use gloves in a sporadic pattern. [37] Gloves will reduce the amount of blood exposure introduced by injury,

especially when caused by a hollow bore needle.[50] Glove use itself has been shown to reduce the risk of injury significantly, and double gloving reduces injury even further.[51]

Double-gloving: The CDC, AORN, OSHA and other authorities agree: wearing 2 pairs of gloves reduces infection risks by providing additional protection if the outer glove is punctured or damaged. Colored under-gloves make any damage immediately visible. Double-gloving may reduce sensitivity and dexterity, so thinness plays an important role, as does texture. [51] A glove with a smooth or lubricated inner surface may be easier to wear as an outer glove over the first glove.

Hand Hygiene and Eye Protection: Influenza A can exist on hands for over an hour with minimal reduction. Soap and water or alcohol-based agents can eliminate all traces.[52] Hand hygiene combined with mask use has been shown to reduce influenza transmission (35-51% reduction).[53] The transocular route may be a significant route of transmission for respiratory agents and influenza is highly efficient by this route.[54] Use of a face shield may prevent contamination of a respirator mask as well as protect the eyes of HCP. [53]

Masks, Respirators, and Airway Protection: The assigned protection factor (APF) is a value given or assigned to each respirator by OSHA and NIOSH. The value indicates the factor that a respirator decreases contaminating/infectious substances in the ambient air. The value is derived from C_O/C_I (concentration out/in) divided by 25, which gives a value of 10-10,000. The number indicates the minimum factor by which exposure is reduced with the respirator (higher is better). N95 means the wearer will get no more than 1/10 of the hazardous particles present. powered air purifying respirators (PAPR) are required to have an APF of 1000+.[55] (Fig. 5)

Two types of devices are commonly used to prevent transmission of airborne infectious agents, medical masks, and respirators.[56] Masks are designed to keep droplets from coming in contact with the face and mucosa of the wearer. They are not fitted and not designed to filter small airborne infectious agents. Respirators are medical devices designed to protect the wearer from airborne infectious aerosols. Respirators work by filtering the airborne particles (air-purifying respirator) or by supplying clean air (atmosphere –supplying respirator).

Air Respirators are further classified into the efficiency of particle removal (95%, 99%, and 100%), N-No oil resistance, R-Oil resistance, P-Oil resistant. Type 100, is 99.97% efficient and costs around $10-$50. Type 99, are

99% efficient and cost around $10. The 95, which are 95% efficient, cost around $0.60-$2. Controversy exists whether there is any benefit of wearing N95 respirators in influenza or other pandemics. (N95 vs. Medical Mask for influenza in nurses, approximately 23% in each group).[57] Many simulation studies support N95 mask use, however, cost remains an issue. (Fig. 6)

The Canadian Biosafety Standards and Guidelines note: "Using the wrong respirator or misusing one can be as dangerous as not using one at all". [58] HCP should wear N95 respirators when performing aerosol-generating procedures, as well as when managing patients with TB, high-risk situations in SARS cases, and in situations where high-risk pandemic influenza exits. [57] Some bodies support the use of more aggressive respiratory protective measures, such as a PAPR for very high-risk procedures (intubation and bronchoscopy).[59] In the situation of low-risk seasonal influenza, a medical mask is recommended to reduce transmission.[60] In one airplane study involving people wearing medical masks, transmission was shown to be signficiantly reduced (0% vs. 50% control).[61]

N95 masks have numerous problems. Breathing resistance can be uncomfortable, and prior fit testing does not assure success in attaining a seal during regular use. Regular users appear to have greater success in maintaining a seal. The reuse of N95 (Not soiled, creased, damaged, moist or wet) is discouraged but permissible if supplies are limited. Disease particles do not normally reaerosolize from the N95, however, it can act as a surface for fomites. A fluid resistant N95 should be used in a surgical setting. If a respirator is going to be reused, it should be stored in a paper bag, and not plastic to avoid condensation. [62-65]

Ultimately, in the laboratory setting N95 masks appear to offer more protection than medical masks but far less than PAPRs. Real world protection is not clear at this time.[66] An N95, combined with face/eye protection appears to be one of the best ways to avoid viral transmission. [53] Two large RCTs have shown that N95 respirators can reduce respiratory infection rates in HCP.[67,68] A study of bacterial colonization demonstrated a rate of 2.8% in HCP who wore N95 respirators; 5.3% in those who wore medical mask and 7.5% in the control group. Co-infections with bacteria and viruses were also reduced. In contrast, it was suggested that medical masks may actually increase the risk of respiratory co-infections (NS but trended).[69] In another study on high-risk respiratory wards, HCP were infected more often when using self-identified risks as an indication to wear a respirator rather than continuous use of a respirator while on duty on that ward. This indicates HCP are not able to predict when they are truly at risk. [67]

Powered Air Purifying Respirator (PAPR): PAPRs have a higher level of protection than N95 masks.[70] They also provide maximum protection without concern for fit or leak. [69] They can be used with glasses or anyone with a face that does not fit well in a simple face respirator.[71] PAPRs use a HEPA filter (99.97% efficient) and have an air-flow greater than 170 L/min. Their cost is around $1000 per unit. They are not disposable and require proper maintenance and cleaning. [69] PAPRs can interfere with tasks and intubations, and the drape may become easily contaminated. [70] In the setting of significant risk, they may provide the greatest degree of protection.

SUMMARY

Prevention of transmission of diseases to HCP requires a multifaceted approach. Strong surveillance for new diseases or diseases in an early stage can often be missed. It is the responsibility of the administration to make sure accepted infection controls and equipment are in place, and the structure of the hospital is acceptable for the care of potentially infectious patients. Consistent with that same concept is the need for effective and frequent environmental cleaning. Additionally, HCP can help protect themselves through several steps, including getting vaccinated where possible, using the correct PPE at the right times, and following infection control protocols. Finally, while we have heard about it over and over for many years, the importance of hand hygiene is still often overlooked. The simple task of washing your hands may not only save the life of a patient, it may also save the life of a HCP.

Questions:

1) Which of following factors appears to play a significant role in a HCP not utilizing protective measures effectively?
    a. Long duty hours and stressful situations (correct answer)
    b. Prior education and orientation
    c. Familiarity with the infectious agent
    d. Not wanting to appear afraid
2) Which of following is NOT associated with an increased chance of an infection resulting from a needlestick injury|?
    a. Hollow bore needle
    b. A deep needle puncture
    c. Double gloving (correct)
    d. High viral load in the patient
3) Choose the INCORRECT answer concerning post-exposure prophylaxis (PEP).
    a. PEP should begun as soon as possible after exposure
    b. PEP should be held until is it confirmed that the patient has active disease. (correct)
    c. PEP may still be effective in some instances even if delayed by days.
    d. Live vaccines should not be used in pregnant women for PEP.

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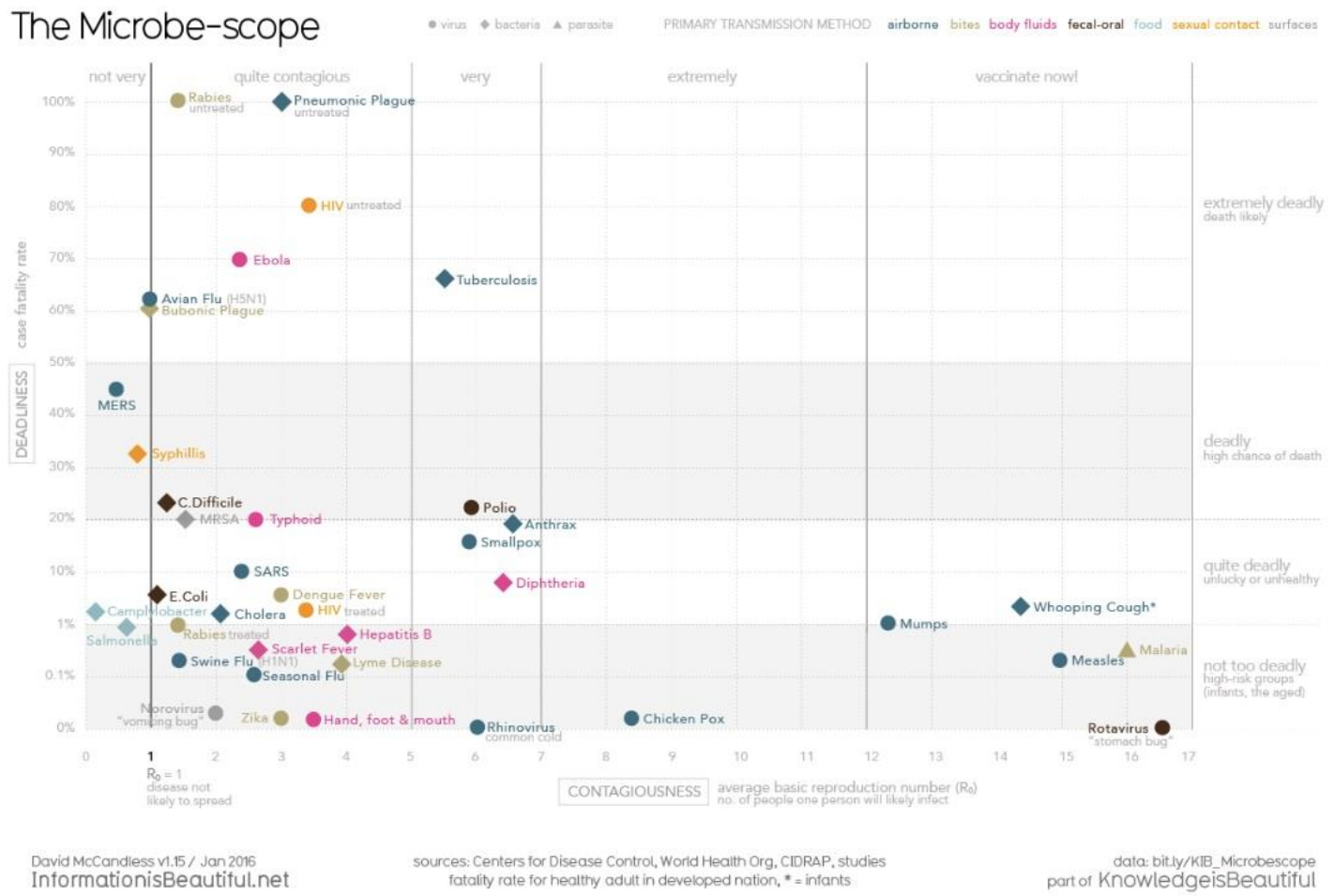

Figure 1: This graphic demonstrates contagiousness vs. mortality. As you move towards the upper areas and to the right, diseases become more lethal and more infectious. (This image is courtesy of David McCandless from Information is Beautiful (available at http://www.informationisbeautiful.net) and the image is reproduced with permission).

Recommended PEP for HBV Exposure				
HCP Status	**Unvaccinated**	**Previously Vaccinated**		
		Responder [1]	**Nonresponder [2]**	**Unknown Antibody Response**
Source HBsAg Positive	Hepatitis B immune globulin X 1 and initiate HBV vaccine series.*	No treatment	1. Hepatitis B immune globulin immediately, 12 hours preferably after exposure. Repeat immune globulin at 4 weeks.[++] 2. Revaccination series + Hepatitis B immune globulin, at different site. 3. Continue HBV vaccine series.	Test for Anti- HBsAg antibody 1. Responder = No treatment 2. Nonresponder = Hepatitis B immune globulin and vaccine booster. 3. Consider testing HBsAg.
Source HBsAg Negative	HBV Vaccine series*	No treatment	1. No acute treatment. 2. Consider Revaccination	No treatment
Source Unknown	HBV Vaccine series*	No treatment	High Risk sourse without capacity to test for Anti-HBs, treat as if HBsAg positive.	Test for Anti- HBs

Figure 2: Postexposure Prophylaxis following Occupational Exposure to Hepatitis B Virus (HBV).

*3 Doses of HBV Vaccine.
[1] Responder: serum levels of anti- HBs > 10 m IU/mL.
[2] Nonresponder: serum levels of anti- HBs < 10 m IU/mL.
[++] Consider this option for nonresponders who have not completed a second 3-dose vaccine series. If vaccine series completed but nonresponder, 2 doses of Hepatitis B inmmune globulin are preferred.
Table adapted from:
The Mountain Plains AIDS Education and Training Center University of Colorado. (2014). PEP Steps: A Quick Guide to Post-exposure Prophylaxis in the Health Care Setting - March 2014. *HIV Provider References Series.*

HCV Serial Testing and Follow Up			
Status Source Blood	HCV Ab Positive	HCV Ab Negative	Unknown or not Available
Labs	Post exposure: HCV Ab, HCV RNA, ALT. No recommendations for HCV PEP available.	HCV Ab	HCV Ab
Follow up and Serial Testing	Exposed HCV should receive appropriate counseling, serial testing and follow up. 4-6 weeks: repeat HCV RNA 6 months: repeat HCVAb, HCV RNA, ALT *If seroconversion to HCV arise, refer patient for management of acute infection.*		Follow up + serial HCV Ab testing

Figure 3: Serial Testing and Follow up following Occupational Exposure to Hepatitis C Virus (HCV).

Table adapted from:
The Mountain Plains AIDS Education and Training Center University of Colorado. (2014). PEP Steps: A Quick Guide to Post-exposure Prophylaxis in the Health Care Setting - March 2014. *HIV Provider References Series.*

<table>
<tr><th colspan="6">HIV Postexposure Prophylaxis (PEP) Regimens</th></tr>
<tr><th>Preferred HIV PEP Regimen</th><th colspan="2">Alternate HIV PEP Regimen

Combine 1 drug or drug pair from the left column with 1 pair of nucleoside/nucleotide reverse-transcriptase inhibitors from the right column</th><th>Alternative Retroviral Agents

Use as PEP only with expert consultation</th><th>Antiretroviral Agents

Not recommended for PEP</th><th>Antiretroviral Agents contraindicated as PEP</th></tr>
<tr><td rowspan="2">Raltegravir 400 mg PO BID
+
Truvada[1] 1 tab PO OD</td><td>Raltegravir
Darunavir
Ritonavir
Etravirine
Rilpivirine</td><td>Truvada
(tenofovir + emtricitabine) -OR-
Combivir [2] (zidovudine + lamivudine)</td><td rowspan="2">Abacavir
Efavirenz
Enfuvirtide
Fosamprenavir
Maraviroc
Saquinavir
Stavudine</td><td rowspan="2">Didanosine
Nelfinavir
Tipranavir</td><td rowspan="2">Nelfinavir</td></tr>
<tr><td colspan="2">Stribild

Complete fixed-dose combination regimen. No additional antiretrovirals are needed (elvitegravir, cobicistat, tenofovir DF, emtricitabine)</td></tr>
</table>

Figure 4: Postexposure Prophylaxis Regimens following Occupational Exposure to Human Immunodeficiency Virus (HIV).

[1] Truvada = single tablet combination tenofovir DF 300 mg + emtricitabine 200 mg.
[2] Combivir= single tablet combination zidovudine 300 mg + lamivudine 150 mg.
Table adapted from: The Society for Healthcare Epidemiology of America. (2013). Updated US Public Health Service Guidelines for the Management of Occupational Exposures to Human Immunodeficiency Virus and Recommendations for Postexposure Prophylaxis. *Infection control and hospital epidemiology, 34*, 9, 875-892.

N95 Respirator

N99 Respirator

N100 Respirator

Figure 5: This figure shows respirators at the higher levels of protection, N-95, N-99 and N-100. For several reasons, in high-risk situations, an N-95 is usually preferred. If a Health Care Provider (HCP) is at extremely high risk for encountering a deadly infection then use of a Power Air Purifying Respirators (PAPR) should be considered.

Power Air Purifying Respirators (PAPR)

Figure 6: Power Air Purifying Respirators (PAPR) afford the highest level of protection for HCP when dealing with infectious agents that can be transmitted through the air.

ANESTHESIOLOGY 2017
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Common Neonatal Emergencies: You Can Never be Better Prepared

Mary Ellen McCann, M.D. **Boston, MA**

Introduction

The first year of life is very vulnerable period with approximately two thirds of infant deaths occurring in the first month of life.[1] The leading cause of mortality in infants in 2011 was congenital anomalies at a rate of 126.1/100,000 births followed by premature births at a rate of 104/100,000 live births.[2]. Although all organ systems are affected by perioperative alterations in physiology, the neurologic system in particular may be susceptible to neurotoxic and ischemic damage during general anesthesia (Table 1). In this brief review, we will discuss some of the relevant anesthetic concerns in surgical neonates.

Prematurity

Closed claim analysis studies have revealed that neonates and infants are at higher risk for morbidity and mortality than any other pediatric age group, mostly because of respiratory and cardiac related events.[3, 4] When assessing the anesthetic risks of young infants, it is important to classify them as neonates who are in their first month of life or infants who are in the first year of their life. Furthermore, the risk of anesthesia is greater in preterm those that are less than 37 weeks postmenstrual age (PMA). Infants who were born preterm but have reached a chronological age that makes them greater than 37 weeks PMA are considered ex-preterm infants. These distinctions are important when determining which infants are appropriate for ambulatory cases. The rates of prematurity have risen recently in the United States and developed world, in part, because of a higher incidence of multiple births and maternal older age. Infants born with congenital anomalies are more likely to require both surgical procedures and to have concomitant congenital cardiac defects, which can complicate the conduct of anesthesia.

Cardiac function is limited and is heart rate dependent in healthy newborns because the immature myocardium has limited compliance.[5] Therefore, bradycardia must be aggressively treated to ensure adequate systemic and cerebral perfusion. A very common cardiac abnormality in premature infants is patent ductus arteriosus (PDA), which can lead to either left to right or right to left cardiac shunting depending on the pulmonary vascular resistance. It is customary to place two pulse oximeters on infants with a known PDA or who are at risk for a PDA to measure preductal (right upper extremity) and postductal (left upper and both either lower extremity) oxygen saturations during surgical procedures. Intraoperative hypoxia, hypercarbia, acidosis, hypothermia, and surgical stress can lead to ductal reopening. Neonates may need vasopressors such as dopamine or additional fluids to maintain normotension during general anesthesia. The parasympathetic system is predominant in preterm and term infants; thus stimulation of the vagus nerve by laryngoscopy or the stress of hypoxia can cause bradycardia. Many pediatric anesthesiologists will routinely administer an anticholinergic agent before manipulating the airway of a neonate.

The respiratory system is also affected by prematurity. Although the type II pneumocytes begin to differentiate by 24 weeks gestation, adequate surfactant is not created until about 34-36 weeks gestation. Maternal treatment with betamethasone before birth and the administration of surfactant immediately after birth improves respiratory mechanics but many preterm infants still require respiratory assistance

such as additional oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation.[6] Preterm infants have a very rate of high oxygen consumption (more than twice that of adults per body weight) and low pulmonary functional residual capacity. Therefore they are at high risk for oxygen desaturation with any interruption of ventilation. Anesthetic inductions can be complicated by tracheomalacia, which makes mask ventilation difficult. Furthermore indiscriminant mask ventilation can result in abdominal distension, which in turn impedes diaphragmatic excursion.

Premature infants are risk for postoperative apnea after general anesthesia with a reported rate between 5-50 % depending on the method of measuring apnea.[7] Studies using clinical measures such as nursing observation with or without impedence pneumonography report rates between 5-10% with anemia, lower gestational age and length of surgery all being risk factors.[7] A recent paper published as part of the GAS project in 2015 found that the risks of early postoperative apnea during the first half hour in the postoperative care unit (PACU) were higher in premature and expremature infants exposed to sevoflurane general anesthesia compared with regional anesthesia.[8] However, there were no differences in risk of postoperative apnea between general anesthesia and regional anesthesia groups between one half hour and 12 hours postoperatively and premature and expremature infants were at increased risk for postoperative apnea. This large study showed that premature and expremature infants need to be observed postoperatively regardless of whether they underwent general or regional anesthesia. Although a prior history of apnea was a risk factor for postoperative apnea, there were infants in this study in both the general anesthesia and regional anesthesia group who developed postoperative apnea who did not have an immediate prior history of apnea. Other earlier studies in which the infants underwent halothane anesthesia have suggested that regional anesthesia has a lower rate of postoperative apnea but regional anesthesia supplemented with sedatives has a reported rate of postoperative apnea greater than general anesthesia alone.[9, 10] Since neonates can have obstructive, central or mixed apnea with most episodes occurring in the first 12 hours postoperatively, most pediatric anesthesiologists recommend at least a 12 hour apnea free period before discharge for former preterm infants who have undergone surgery.[11] The risk of postoperative apnea persists until the infants reach a postmenstrual age of 60 weeks.[7, 8]

Preterm infants are also at risk for retinopathy of prematurity, a progressive overgrowth of retinal vessels, which can lead to intraocular hemorrhage, retinal detachment and blindness. Although it has been reported in term infants who were not given supplemental oxygen, it is typically found in preterm infants exposed to supplemental oxygen.[12] It is important for anesthesiologists to limit the inspired oxygen for preterm infants less than 46 weeks postmenstrual age and aim for oxygen saturation percentage in the range of low to mid 90s.[12]

The immature renal and hepatic systems affect fluid and electrolyte management and alter the metabolism of common anesthetic medications and antibiotics during the perioperative period. Neonates have a lower glomerular filtration rate and urine concentrating ability. This leads to impaired renal clearance of solutes and drugs. Drug metabolism and protein binding are also diminished due to immature hepatic function in the neonate. Therefore it is also important to regulate the fluids and drugs administration carefully in these patients.

The surface area of neonates is larger per body weight and thus they are susceptible to evaporative losses both through surgical wounds as well as their skin and their renal system is unable to concentrate their urine to compensate for fluid losses. The larger surface area also puts neonates and premature infants at higher risk for significant temperature fluctuations during surgical procedures. Hypothermia can stress the infant leading to respiratory failure and the need for postoperative ventilation. On the other hand, it is important to not overheat premature infants while in the operating rooms.

Neurotoxicity

General anesthetics in vivo and in vitro experiments have been shown to have neurotoxic effects on developing central nervous system. In December 2016 the FDA published a warning about repeated or lengthy use of general anesthetic and sedation drugs in children less than 3 years of age because of concerns that these drugs may affect the child's developing brain. These potential effects include decreased neurogenesis, abnormal dendrite formation, decreased glial cell formation and increased in neuroapoptosis in both the brain and spinal cord.[13-15] Neuroapoptosis or programmed cell death occurs normally during fetal development as part of cerebral and neuronal maturation. However, anesthetic exposure during vulnerable periods in laboratory animal has been shown to lead to a marked increase in apoptotic cell death and subsequent learning deficits especially in the domain of executive function in animals allowed to mature. The general anesthetics found to cause this neurotoxicity include most of the commonly used agents such as those that block N-methyl-D-aspartate (NMDA) glutamate receptors (ketamine, nitrous oxide) and those that are gamma amino butyric acid (GABA) agonists (volatile anesthetics, benzodiazepines, barbiturates). The period of maximal vulnerability to the neuroapoptotic effects of anesthetics in animals seems to correspond with the time of maximal synaptogenesis. For rodents this is day 7 of life, for rhesus monkeys this is day 122 of gestation up to day 5 of life with no excessive apoptosis seen on day 35.[16, 17] The neurotoxic effects of anesthetics on animals are also dose and duration dependent. Extrapolations of these preclinical studies to humans are fraught with uncertainty because of physiological differences between species and difficulties in physiologic monitoring for glucose, blood pressure and respiration in very young, small mammals. Several studies have been published recently specifically examining whether the receipt of general anesthesia in infancy is associated with later learning difficulties.[18-25] The findings of these studies are mixed with a slight preponderance of retrospective cohort studies showing an association with receipt of anesthesia in early life with later neurocognitive problems. Confounding by indication is very difficult to control for in these studies. Two recent large cohort studies from Canada revealed that there was a slight excess risk of neurocognitive problems in children exposed to anesthesia between the ages of 2-4 but no increased risk in children exposed to anesthesia before the age of 2.[24, 25] The PANDA study published in 2016 –an ambidirectional study examining short procedures in children exposed to anesthesia before the age of 36 months found that general anesthesia exposure was not a risk factor for poor neurocognitive outcomes.[26] The only prospective study comparing general anesthesia with regional anesthesia for hernia repair in early infancy, the GAS study did not find a difference in neurocognitive outcomes for their interim outcome at age 2.[27]

General anesthesia may cause both neurotoxic and ischemic damage in neonates.[28] The urgent nature of many of the surgeries as well as physiological changes that neonates undergo especially in the first few days of life leave many infants in suboptimal condition for general anesthesia. Difficulties in accurately measuring end-tidal CO_2, blood pressure, pH, blood glucose and oxygen saturation levels can delay necessary interventions for these fragile patients. In general, these infants have less reserve and thus small alterations in blood pressure can lead to inadequate cerebral perfusion if the infant becomes hypotensive or increase the risk of intraventricular hemorrhage if the infant becomes hypertensive.[29] Periods of hypocarbia and hyperoxia in infants with hypoxic ischemic injury are associated with increased morbidity and death and may be a risk factor for outcomes after general anesthesia because of decreased cerebral perfusion.[30-32] Even mild hyperthermia *in utero* just prior to delivery or after a hypoxic ischemic injury is associated with poor neurologic outcomes but the risk for anesthetized infants is unknown.[33-35] Hypoglycemia and hypoxia in infants under general anesthesia may be a risk factor for poor development.[36]

Specific Conditions: (Table 2)

Tracheoesophageal Fistula (TEF)

The incidence of esophageal atresia with tracheoesphageal fistula (TEF) occurs approximately 1/3000 live births. The most common type of presentation occurring 87% of the time is an esophageal atresia with distal TEF (Table 3). Infants present with copious salivation, and choking/coughing with the onset of feeding. TEF is also seen as part of the VACTERL association (vertebral anomalies, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities). The mainstay of anesthetic management of these infants is to isolate and block the fistula prior to positive pressure ventilation. This can be done with a Fogarty catheter insertion by the surgeon while doing a rigid bronchoscopy. Sometimes it is possible to pass an endotracheal tube past the fistula into the right main stem bronchus if a bronchial blocker is not feasible. Initial surgical treatment can include gastrostomy, fistula repair, spit fistula, central line placement and the Foker procedure for long gap esophageal atresia.

Gastroschisis and Omphalocele

These diseases are caused by defects in the abdominal wall leading to the intestines being outside abdominal cavity. In the case of omphalocele, the intestines are encased in a thin layer of tissue. The prevalence of gastroschisis is approximately 1/2000 live births and omphalocele is approximately 1/4000 live births. Gastroschisis is usually an isolated congenital anomaly that is increasing in prevalence especially with younger maternal age. Infants born with gastroschisis and omphalocele are at high risk for infection, dehydration and hypothermia and generally are surgically managed emergently. Omphalocele are associated with genetic abnormalities such as trisomies 13, 18, and 21 and Beckwith-Wiedemann Syndrome. Infants with Beckwith Wiedemann Syndrome have large tongues which can complicate endotracheal intubation and are at risk for hypoglycemia secondary to hyperinsulinemia. Infants are mostly either primarily repaired or the abdominal contents are placed in a silastic silo which is cinched every day to incrementally move the intestines into the abdominal cavity (Figure1). Very often these infants require postoperative ventilation with muscle relaxation to allow their abdominal cavity to accommodate their intestines. Infants with intact omphalocele membranes can be also treated medically. It is possible to paint the membranes periodically with a silver sulfadiazine solution which shrinks the omphalocele gradually.

Pulmonary Hypoplasia and Congenital Diaphragmatic Hernia (CDH)

Congenital diaphragmatic hernia occur in approximately 1/2000 live births. This condition is always accompanied by pulmonary hypoplasia due to a decrease in the cross-sectional area of the pulmonary vasculature. The mortality rate is very high-approaching 50% despite intensive treatment. Treatment consists very often of endotracheal intubation and extracorporeal membrane oxygenation (ECMO) initially. Often the diaphragm is repaired while the infant is on ECMO. Ventilatory strategies for conventional ventilation include permissive hypercapnia to reduce barotrauma to the lungs. Up to 40% of these infants may have congenital heart disease which leads to a poorer prognosis. These infants are often treated with vasopressors to maintain their blood pressures and vasodilators (nitric oxide) to improve their pulmonary hypertension.

Necrotizing enterocolitis (NEC)

Necrotizing enterocolitis is usually seen in extremely premature infants (less than 1500 g) who are on oral formula feeds. Radiographic finding may include pneumatosis intestinalis, abdominal free air, distended loops of bowel and intraperitoneal free fluid. Symptoms may be subtle with an increase in apnea and bradycardia, anemia and delayed gastric emptying. Later signs include increasing abdominal girth, diarrhea, respiratory failure and shock. The mortality for this disease is very high. Treatment initially is bowel rest with intravenous nutrition and antibiotics. Infants with evidence of bowel perforation are

usually treated surgically but in some cases can be managed with interventional radiologic placement of drains.

Inguinal Herniorrhaphy

Inguinal hernias are one of the most common surgical conditions seen in neonates occurring in about 1-5% in full term infants and up to 30% of preterm infants.[37] This condition is much more common in males compared with females. Repair can be done either open, laparascopically or open with laparascopic peak on the contralateral side to the presenting hernia. About 10% of infants with a unilateral hernia will be found to have an occult hernia on the contralateral side. All types of surgical repairs can be accomplished with general anesthesia. Regional anesthesia alone can be done in open or open with laparoscopic peaks procedures. Pain management postoperatively can be accomplished with an intraoperative caudal regional block or ilioinguinal peripheral nerve block.

Pyloric Stenosis

Infantile hypertrophic pyloric stenosis is most commonly seen in first born male infants between the ages of 2 and 6 weeks of age. It is characterized by severe non- bilious vomiting which can lead to a hypochloremic metabolic alkalosis. Physical signs include a palpable mass ("olive") above the umbilicus. Surgery (laparoscopic or open) should be done after the electrolyte disturbances and dehydration have resolved. In rare cases it can be treated medically with intravenous and oral atropine.

Minimally Invasive Surgery

. The advantages of this technique include smaller incisions, shorter postoperative recoveries and less postoperative pain. However, these cases can be highly challenging for anesthesiologists. Thoracic procedures in newborns include procedures for lung resections and biopsies, congenital diaphragmatic repair, tracheal esophageal fistula and atresia, patent ductus arteriosis and repair of mediastinal masses. The incidence of late postoperative scoliosis is increased in neonates who have had open thoracotomies.[38]

Single lung anesthesia in newborns can be accomplished with placement of a bronchial blocker (usually a Fogarty catheter) either passed through or beside an endotracheal tube into the mainstem bronchus of the ipsilateral lung using bronchoscopy to verify its position. Visualization of the pleural space around the partially collapsed lung can be augmented by low flow and low pressure insufflations of CO2. Many of these cases are associated with hypotension, respiratory acidosis, hypercapnia and hypothermia. Rarer complications include CO_2 embolus and pneumoperitoneum.[39] A retrospective review of congenital diaphragmatic hernia repairs done thorascopically in neonates demonstrated a 50% incidence of decrease in oxygen saturations and rise in endtidal CO_2.[40] These changes were managed by increasing minute ventilation, decreasing insufflating CO_2 flow rate and pressure and maintaining denser neuromuscular blockade. A pilot randomized controlled trial in 20 infants >1.6 kg undergoing CDH or esophageal atresia repair done either by open thoracotomy or thoracopically found that there was significantly more respiratory acidosis and hypercapnia in CDH patients done thorascopically.[41] However, the esophagael atresia patients did not have significant changes in endtidal CO_2, pH or O_2 saturation.

Laparoscopic surgical approaches can be used for pyloromyotomy, gastrostomy, fundoplication, gut malrotation, duodenal atresia, ovarian pathology, Hirshsprungs Disease pull-through, imperforate anus and inguinal herniorrhaphy. In neonates, surgeons often must access the umbilicus through an open techique because of a retained umbiical stump and the danger of inadvertent tissue damage from blind trochar insertion into the tiny abdominal cavity. It is necessary to develop a pneumoperitoneum in order for clear visualization of the abdominal organs. The most commonly used method is low pressure insufflation of CO_2 which typically leads to higher levels of endtidal CO_2 and respiratory acidosis in neonates compared with older individuals. It is advised to maintain the intracavitary pressure at or below 10 mmHg to avoid undue cardiovascular effects in neonates. Higher pressures can lead to reduced venous return to the heart and hypotension and difficulties in ventilation if the diaphragm is unable to fully descend into the abdominal cavity. Maintaining adequate hydration is also key in avoiding intraoperative hypotension and neuromuscular blockade will facilitate ventilation.

Neuroendoscopic procedures for cranial suture synostosis and hydrocephalus have been found to decrease hospital stays and need for transfusions.[42] Endoscopic third ventriculostomy can be accompanied by acute bradycardia that may be part of a Cushing's reflex or by direct stimulation of the ventricular floor. Acute elevations in intracranial pressure even in newborns with open fontanelles can be caused by a mechanical disturbance of egress of irrigation fluid. Small amounts of intracranial hemorrhage must be managed by copious amounts of irrigation fluid that can also lead to hypothermia. Since neonates and preterm infants skulls are too thin for fixation pins, neuromuscular blockade is essential to prevent movement during delicate neurosurgery.

Regional anesthesia

Regional anesthesia used as an adjunctive agent can reduce the amount of general anesthesia exposure a neonate received during major abdominal and thoracic surgery and can also be used to ensure postoperative analgesia. Pure regional anesthesia (either spinal or spinal with epidural or epidural alone) has been used for inguinal herniorrhaphies, PDA, gastrostomy, pyloromyotomy, bladder extrophy, anoplasty, omphalocele, circumcision and orthopedic surgery. The distal end of the spinal cord in neonates is generally between L2 and L3, so pediatric anesthesiologists place a 22 or 25 gauge needle below this interspace to achieve spinal anesthesia. Neonates have more spinal fluid per body weight compared to adults and require a larger dose per body weight and the duration of neuromuscular block is shortened. Local anesthetic toxicity is a greater concern in neonates because the bound fraction of agent is decreased secondary to low levels of alpha-1 acid glycoprotein in neonates and because of decreased clearance and elimination half-life. Ester local anesthetics such as 3-chloroprocaine are metabolized by plasma pseudocholinesterase rather than the liver. These may be a safer option for very young neonates that require ongoing local anesthetic infusions for anesthesia. Lidocaine, ropivacaine and levobupivacaine are associated with less cardiotoxicity than bupivacaine and thus are preferred by some institutions.[43] Intravenous intralipid (20% in a dose of 1 ml/kg given every 3-5 minutes for a total dose of 3 ml/kg) can be lifesaving in infants manifesting malignant ventricular dysrhymias from local anesthesia toxicity.[43]

The rate of spinal anesthesia success varies between 78-89% in single institution series.[44-47] A recent multicenter study comparing the effects of general anesthesia versus regional anesthesia in infants less than 60 weeks postmenstrual age found that surgical times did not vary between the two techniques but that the over all operating room time and anesthesia time was greater in the general anesthesia group.[48] Adjunctive single shot caudal epidural or epidural with a catheter can be used in awake or anesthetized infants to prolong the effects of a spinal anesthetic.

The most common approach for epidural anesthesia in anesthetized neonates undergoing major abdominal or thoracic surgery is caudally. Catheters can be threaded into the thoracic epidural space for

surgeries involving the thorax and abdomen and into the lumbar space for lower pelvic and limb surgeries either using ultrasonography or epidurography for accurate placement. Advantages of adjunctive epidural analgesia postoperatively include quicker times to extubation and greater blunting of postoperative stress responses. Important disadvantages to keep in mind include that the highest success rates in threading epidural catheters to the thoracic space are with adult size catheters which may be too large for premature infants. In a study of 20 infants with weights ranging between 520 grams to 2750 grams using a smaller specially designed 23 guage neonatal catheter, there was a success rate of 85%. In this small series, malpositioned catheters ending up in epidural vessels, intrathecally and curled up in the lumbar space.[49]

Although there are theoretical benefits to regional anesthesia such as better analgesia, decreased stress response, earlier postoperative extubation, and less general anesthetic exposure, there is little published evidence that clearly demonstrate an improvement in care.[9, 50, 51] The risks of regional anesthesia in neonates and premature infants is also not well characterized at this time. The Pediatric Regional Anesthesia Network database in the US has tracked the outcomes of nearly 15,000 regional anesthetics since 2007 without significant morbidity or mortality found in neonates although the number of neonates followed is small.[50, 52] There are isolated case reports of meningitis, spinal fluid leak and total spinal anesthetics in neonates under going spinal anesthetics.[53, 54]

Summary:

Ongoing advances in the perioperative management of the neonate have undoubtedly decreased the incidence of morbidity and mortality of this vulnerable group. The introduction of new surgical techniques and more comprehensive understanding of the effects of anesthetic drugs and techniques on the surgical neonate present many challenges to surgeons and anesthesiologists. Many conditions are unique to small children. Thorough preoperative evaluation and open communication between members of the health care team are important. A basic understanding of age-dependent variables and the interaction of anesthetic and surgical procedures are essential in minimizing perioperative morbidity and mortality.

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Table 1. Common Prepartum and Perinatal Conditions associated with Neonatal Morbidity

Condition	**Perioperative Problems**
Asphyxia	• Depressed myocardial function • Hypoglycemia • Electrolyte abnormailites • Impaired cerebral autoregulation • Decreased gut perfusion • Shock • Coagulopathy
Infants of diabetic mothers	• Hypoglycemia • Hypocalcemia • Polycythemia
Prematurity	• Hypoglycemia • Respiratory distress syndrome • Postoperative apnea • Retinopathy of prematurity • Temperature instability
Small for gestational age	• Hypoglycemia • Hypocalcemia • Polycythemia and hyperbilirubinemia • Temperature instability • Congenital anomalies • Increased incidence of pulmonary aspiration/pneumonia
Large for gestational age	• Birth injuries (brachial/phrenic nerve, fractured clavicle) • Hypoglycemia • Hypocalcemia • Polycythemia and hyperbilirubinemia • Meconium aspiration

Figure 1.

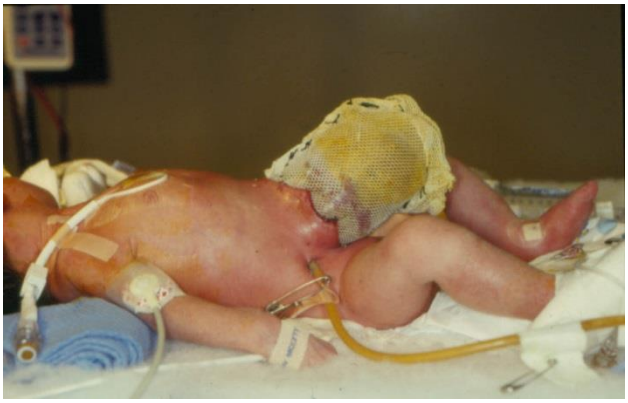

Table 2. Perioperative Considerations for Complex Neonatal Surgery.

Surgical Diagnosis	**Preoperative Considerations**	**Intraoperative Considerations**	**Postoperative Considerations**
Gastroschisis and Omphalocele	RDS if premature Cardiac anomalies in omphalocele Sepsis Intestinal atresia Hypovolemia Hypoglycemia (Beckwith-Wiedemann)	Hypovolemia Hypothermia Hypercarbia Hypoxemia Respiratory acidosis Metabolic acidosis Atelectasis Volume overload/pulmonary edema	Oxygenation/Ventilation problems Bowel ischemia Renal Failure Peritonitis Sepsis Metabolic acidosis Hypothermia Epidural for post-op analgesia
CDH	Over-expanded contralateral lung Hypoplastic ipsilateral lung PTX Pulmonary HTN May be on ECMO Respiratory acidosis Metabolic acidosis IVH Hypoglycemia Hypokalemia if on diuretics	Epidural or narcotic-based technique PTX Hypovolemia Pulmonary HTN Suprasystemic RVBPs Hypoventilation Hypothermia Metabolic acidosis R-to-L shunting Volume overload	Epidural for post-op analgesia PTX Hypovolemia Pulmonary HTN Suprasystemic RVBPs Hypoventilation Hypothermia Metabolic acidosis R-to-L shunting Volume overload May require HFOV or ECMO after "honeymoon period" within 24-48 hrs or repair
TEF	Aspiration Gastric distention RDS if premature Cardiac anomalies GI anomalies Renal anomalies	Epidural or narcotic-based technique Aspiration Hypothermia Metabolic acidosis Respiratory acidosis PTX Atelectasis/hypoxemia Mucus plugging Gastric distention	Epidural for postop analgesia PTX Apnea Hypoventilation Tracheal leak Weakness RLN injury Pneumonia

		Extubation in OR if possible	
NEC	RDS if premature Sepsis ARDS CHF with cardiac anomalies Pulmonary overcirculation/ pulmonary HTN IVH with prematurity/birth asphyxia Renal insufficiency if on NSAIDs for PDA Hypoglycemia Hypocalcemia DIC	No epidural if septic Minimize FiO2 (ROP) Pressors/ionotropes Hypovolemia Metabolic acidosis PTX Hypoglycemia Hypocalcemia	ROP Hypovolemia Metabolic acidosis Sepsis Pulmonary edema with fluid remobilization Narcotics for postop analgesia

Table 3. Types of Congenital Tracheoesphageal Fistulas and Esophageal Atresia

Anatomic Characteristics	**Percent of Cases (%)**
Esophageal atresia with distal TEF	**87**
Isolated esophageal atresia without TEF	**8**
Isolated TEF	**4**
Esophageal atresia with proximal TEF	**1**
Esophageal atresia with proximal and distal TEF	**1**

Questions:

1. Postoperative apnea :
    a. Is higher after general anesthesia compared to spinal anesthesia 6 hours postoperatively after sevoflurane anesthesia
    b. Risk highest in premature infants born between 32 and 35 weeks gestation
    c. Occurs between 5 and 15 % of the time in premature and expremature infants
    d. Is almost always caused by obstructive apnea rather than mixed or central apnea
2. Pyloric stenosis
    a. is most commonly seen in first born girls
    b. is most commonly associated with hyperchloremic alkalosis
    c. is most commonly associated with hypochloremic acidosis
    d. is never a surgical emergency
3. The most common type of tracheoesophageal fistula is:
    a. esophageal atresia with distal TEF
    b. isolated esophageal atresia
    c. H type fistula
    d. esophageal atresia with proximal TEF

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Mitral Valve Repair: Surgical versus Transcatheter?

G. Burkhard Mackensen MD PhD FASE **University of Washington, Seattle, WA**

Mitral valve (MV) disease remains a significant cause of morbidity and mortality, especially in the elderly population.[1] Mitral regurgitation (MR) as a result of degenerative, functional/ischemic or mixed etiology has a high prevalence in developed countries which increases with age.[2] Traditionally, MV disease was treated with surgical valve repair or replacement while percutaneous treatment was limited to balloon mitral valvuloplasty in the case of mitral stenosis.[3,4] The growing field of transcatheter interventions now includes percutaneous approaches for MR including leaflet and chordae repair, indirect coronary sinus annuloplasty, direct annuloplasty and valve replacement.[5] Major advantages of the transcatheter options for repair include the percutaneous (less invasive) approach (even patients at prohibitive risk for surgery can be treated, faster recovery and shorter hospital length of stay), and the ability to assess the results of the repair immediately and dynamically (beating heart). Surgical mitral valve repair has its own advantages, especially when performed at high volume centers of excellence. Advantages include the significant experience with established operative techniques and large volumes of clinical outcome data associated with the various surgical repair techniques.

The most established and approved transcatheter technique for MV repair in the United States is the MitraClip® system (Abbott, Menlo Park, CA), which mimics the surgical edge-to-edge repair by creating a double orifice valve.[6] To date, more than 35,000 patients have been treated worldwide. Restoring the coaptation between the anterior and posterior MV leaflets with satisfactory reduction of MR can generally be accomplished with the use of one or more MitraClips®, but in more than 40% of patients, at least two MitraClips® are required. Although the surgical MV repair is considered as a "gold standard" in the treatment of MR, compelling long-term outcome data are lacking[7] and a significant proportion of patients are at prohibitive risk for open heart surgery due to their age, reduced left ventricular function, comorbidities and other reasons.[8] The Endovascular Valve Edge-to-Edge REpair STudy (EVEREST) I demonstrated the safety, feasibility and efficacy of MitraClip® procedure in patients with 3 to 4+ MR while EVEREST II randomized cohort results revealed superior safety and similar improvements in clinical outcomes despite residual MR in many patients when compared to surgery.[9,10] The majority of high surgical risk patients had significant reduction in MR (≤2+) leading to improved symptoms and significant left ventricular reverse remodeling at 12 months in the EVEREST II High Risk Study non-randomized cohort.[11] Following the results of these trials, the US Food and Drug Administration (FDA) approved the MitraClip® system in October of 2013 for commercial use in patients with significant symptomatic degenerative MR (≥ 3+) who are at prohibitive risk for surgery.[a]

In an effort to expand the limited FDA indications, the ongoing Clinical Outcomes Assessment of the MitraClip® Percutaneous Therapy for Extremely High-Surgical-Risk Patients (COAPT) evaluates the safety and effectiveness of MitraClip® in functional MR patients when compared to medical therapy (ClinicalTrials.gov Identifier: NCT01626079). In addition to the COAPT trial, The Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy registry with over 9,000 MitraClip® patients, EVEREST II High-Risk registry and REALISM Continued Access Study High-Risk Arm are continuing to enroll MitraClip® patients with functional MR. The initial experience following commercialization in the US demonstrated a favorable success rate that supports the effectiveness of the MitraClip® therapy in high risk surgical patients with degenerative MR. The treatment of functional MR with the MitraClip® remains off-label use reserved for symptomatic improvement in the United States. However, it is currently the most common indication for the MitraClip® therapy in Europe with the international registry data showing good safety record and symptomatic improvement after 1 year.[12-15] Until convincing effectiveness data of ongoing trials and registries are available, the long-term benefits of the MitraClip® therapy in patients with functional MR remain uncertain, a fact which is reflected in recent American Heart Association Heart Failure guidelines.[16]

The MitraClip® procedure requires careful planning and a dedicated team with expertise in cardiac imaging and transcatheter interventions. The structural heart valve team seeks input from an interventional cardiologist, a cardiac

[a] FDA approval of MitraClip Clip Delivery System. Available at: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm375149.htm

surgeon, a cardiac anesthesiologist (who may or may not serve as the interventional echocardiographer) or a dedicated interventional echocardiographer (with or without a sonographer). Cardiac anesthesiologists with experience in perioperative real-time two- (2D) and three-dimensional (3D) echocardiography are ideally positioned to serve the role of interventional echocardiographer.[17,18]

Similar to the surgical MV repair data which indicate that the best outcomes are associated with experienced reference centers,[19] the MitraClip® procedure should be performed by an experienced interventional cardiologist especially in cases with more challenging MV morphology. Some of the optimal MV morphological features for the MitraClip® procedure include regurgitation isolated to the middle (Carpentier's classification 2) segment with minimal leaflet calcification, adequate MV opening area (≥ 4 cm^2), sufficient posterior leaflet length (≥ 10 mm), a flail width of < 15 mm and a flail gap of < 10 mm. Deployment of the MitraClip® is more challenging in Carpentier's classification segments 1 and 3 (due to increased risk of entanglement of the device in the dense chordal apparatus in the commissures), mild leaflet calcification, suboptimal MV opening area (3-4 cm^2) and mobile posterior leaflet length of 7-10 mm.[20]

After appropriate screening and determining that the patient is not a surgical candidate based on consultation with a cardiac surgeon, the MitraClip® procedure is performed with fluoroscopic and more importantly TEE guidance including real-time 3D imaging. In some institutions, fusion imaging (where echocardiographic images and guidance tools are projected onto the fluoroscopy screen) may be available for procedural guidance, but the experience with such imaging is limited.[21] During the procedure, TEE is essential in guiding safe transseptal puncture, advancement of the delivery system, and positioning of the MitraClip®. The MitraClip® has to be positioned perpendicular to the line of coaptation of the MV leaflets and ideally in the center of the regurgitant orifice and regurgitant jet. During and following leaflet grasping and closing of the device, the extent of leaflet insertion and grasp stability need to be assessed. Following deployment of the MitraClip®, 2D and 3D TEE imaging is used to evaluate clip stability, coaptation surface length, residual MR and mitral orifice area .[22] In addition, any complications such as leaflet detachment from the MitraClip®, entanglement in the chordal apparatus, cardiac perforation (tamponade), and large postprocedural iatrogenic atrial-septal defect should be ruled out.

Despite the expanding potential therapeutic targets for the MitraClip® procedure, the long-term sustainability of the national MitraClip® programs will depend on expanding the FDA indications and ensuring appropriate reimbursements for device and procedural costs. The Centers for Medicare & Medicaid Services has recently finalized their proposal to reassign the MitraClip® procedure to a new diagnosis-related group, which will result in a significant increase in the base payment rate. Final payment rates will go into effect October 1, 2016.[c] In November of 2016, Abbott launched a new and updated equipment version termed the MitraClip® NT system. Amongst other features, this new system offers grasping with a fully open MitraClip® and improved steering and handling of the delivery system.

Future perspective

Recent developments in transcatheter MV therapy offer new opportunities for treatment of MV disease. In the future, percutaneous repair options might be combined by adding a transcatheter annuloplasty to the MitraClip® procedure.[23] Advances in 3D echocardiography and hybrid imaging will continue to support the refinement of current technologies, the expansion of clinical applications and the development of novel devices. Growing use of 3D echocardiography to improve patient screening, optimize implantation strategy and identify potential complications offers a unique opportunity for cardiac anesthesiologists to be involved in pre-procedural planning. Furthermore, cardiac anesthesiologist should take a leading role in procedural imaging, which is essential for interventional guidance and assessment of device effectiveness. In addition to expert imaging, the success of the MitraClip® therapy or any other transcatheter valve intervention depends on multidisciplinary input from structural heart valve team with effective and dynamic communication amongst team members. Finally, continuous evaluation of relevant evidence from randomized studies, meta-analyses and registries regarding the safety, short-term and long-term effectiveness of current and new transcatheter devices is critical in justifying the device and procedure costs in the current environment of diminishing reimbursements.

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[c] Final Medicare rule for fiscal year 2017 with new rates effective October 1, 2016 (12% increase in MitraClip Medicare weighted average reimbursement rate). Available at: https://s3.amazonaws.com/public-inspection.federalregister.gov/2016-18476.pdf

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ANESTHESIOLOGY 2017
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Anesthetic Management for Minimally Invasive and Robotic Mitral Valve Repairs

Kent H. Rehfeldt, MD, FASE **Rochester, Minnesota**

The popularity of robot-assisted mitral valve repair (MVR) has grown, in part due to the numerous potential benefits for patients including greater overall patient satisfaction, shorter hospital length of stay, reduced postoperative pain, a faster return to normal daily activities, a lower rate of surgical site infection, and diminished incidence of blood product transfusion. Many surgeons have embraced the robotic approach to mitral surgery due to enhanced stereoscopic vision, the ability to control multiple instruments simultaneously, and increased mobility of the working robotic arms within the chest when compared with traditional thoracoscopic instruments. The practice of robot-assisted MVR is intensive and requires that the anesthesiologist employ numerous subspecialty skillsets including regional anesthesia and analgesia techniques, elements of thoracic anesthesia practice, in particular one-lung ventilation (OLV), cardiac anesthesia, and transesophageal echocardiography (TEE).

Preoperative Planning

Optimal patient results following cardiac surgery requires deliberate communication and planning between all members of the perioperative teams including surgeons, anesthesiologists, perfusionists, nurses, and surgical assistants. This is especially critical prior to robotic cardiac surgical procedures since surgical and anesthetic techniques often differ from the "standard" approach and numerous possible options exist for accomplishing similar goals. The mode and timing of regional anesthesia and analgesia interventions must be determined. The conduct of cardiopulmonary bypass (CPB) must be planned, in particular the number, type, and location of venous cannulae. The means of cardioplegia administration should be delineated. Immediate postoperative disposition should be determined in order to ensure the availability of appropriate personnel and other resources whether this be the intensive care unit (ICU), step-down ward, or recovery room.

Analgesia

Though reduced pain scores have been reported by some, robot-assisted MVR is not pain-free and some investigators have found similar postoperative pain scores whether cardiac surgery is performed by standard sternotomy or using a minimally-invasive approach. An opioid-based, intravenous analgesia regimen may be used for either standard sternotomy or minimally-invasive approaches for mitral valve operations. However opioid-based analgesia regimens are accompanied by troublesome side effects, such as postoperative nausea and vomiting and delayed emergence from anesthesia, the latter potentially confounding attempts to extubate the patient promptly at the conclusion of surgery.

As part of an opioid-sparing approach, a number of regional anesthesia and analgesic techniques may be employed. Potential regional techniques that may be selected include the administration of intrathecal opioids or local anesthetics, thoracic epidural catheter placement, intercostal nerve blocks (ICNB), or paravertebral nerve blocks (PVNB). The local infiltration of long-acting, liposomal bupivacaine into the incisions represents another alternative.

Some anesthesiologists have used intrathecal opioids with good success in patients undergoing cardiac surgical procedures. One possible approach to intrathecal analgesia involves the pre-induction injection of 300 mcg of preservative-free morphine administered as a single shot in the lumbar intrathecal space using a 25 gauge needle combined with a long-acting local anesthetic injected into the incisions at the end of the case by the surgeons. Since no paravertebral block is performed, the surgeon can inject a larger volume of either plain bupivacaine or liposomal bupivacaine at the end of the operation. However, some anesthesiologists are reluctant to utilize neuraxial techniques prior to administration of large doses of heparin.

More recently, we have occasionally utilized pectoralis blocks (Pecs I and Pecs II) and serratus plane block. These blocks are simple to perform with ultrasound guidance and can be performed after the patient is asleep. There is no risk for central spread with resulting sympathectomy and planned opening of the right pleural cavity at surgery reduces the concerns related to pneumothorax. Although there is no literature to date on the use of these blocks for minimally invasive cardiac surgery, the Pecs blocks have been used successfully to treat mastectomy pain.

Although we have occasionally used intrathecal analgesia, pectoralis blocks and serratus plane blocks, the vast majority of patients undergoing robot-assisted MVR at our institution have received pre-induction PVNB (Figure 1). These blocks are performed with ultrasound guidance. While variability in practice exists, we use a series of three, right-sided paravertebral injections, with 10 cc of bupivacaine with epinephrine injected at each

level. Advantages of PVNB include spread of local anesthetic over multiple dermatomes, a reduced risk of neuraxial hematoma in a heparinized patient, as well as a lower risk of hypotension from sympathetic blockade. The inclusion of PVNB into our anesthetic management plan along with the associated decrease in the use of systemic opioid medications has allowed us to extubate almost all patients in the operating room at the conclusion of surgery.

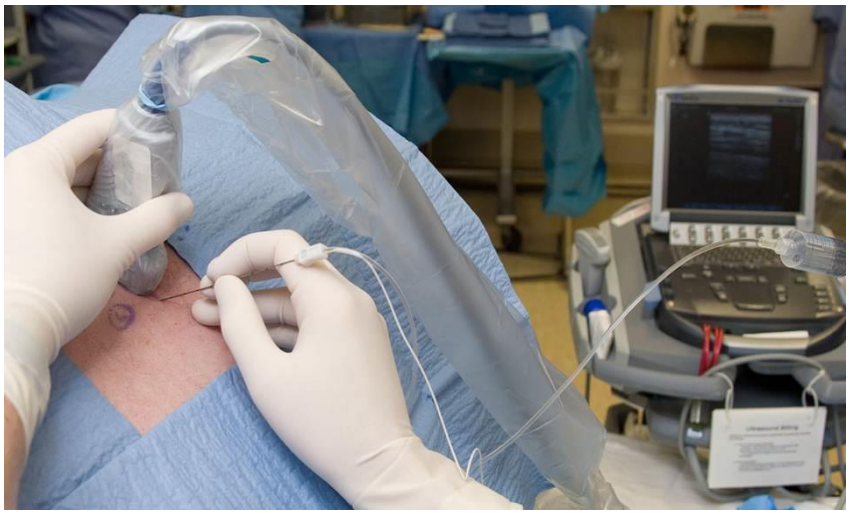

Figure 1. Preoperative, ultrasound-guided paravertebral nerve block prior to robot-assisted mitral valve surgery.

One-lung Ventilation and Capnothorax

Since robot-assisted MVR is accomplished via small incisions and working ports in the right chest, the procedure requires collapse of the right lung, insufflation of carbon dioxide into the right chest, and isolated ventilation of the left lung. Lung isolation may be accomplished by means of either a double-lumen endotracheal tube (DLETT) or the use of a standard, single-lumen endotracheal tube (SLETT) along with a bronchial blocker. We have used both methods, although we favor the use of a left-sided DLETT when feasible. Although initial placement of a DLETT is more challenging, we find it easier to deflate the right lung when compared with SLETT with a bronchial blocker. We have also found that dislodgment of the right-sided bronchial blocker occurs relatively frequently with repetitive inflation and deflation and the right lung, particularly following CPB. Finally, if desired, the application of continuous positive airway pressure (CPAP) to the right lung is more difficult when a bronchial blocker is in place. Nonetheless, placement of a SLETT with a bronchial blocker may be preferred if the patient proves difficult to intubate. Since we extubate almost all patients in the operating room at the conclusion of surgery, the decision regarding changing a DLETT to a SLETT is rarely an issue.

Intraoperative hypoxemia associated with OLV during robotic cardiac surgery is well-documented and has been a frequent occurrence in our practice as well. Hypoxemia tends to be particularly problematic following CPB, even if OLV poses no problem prior to CPB. Increased shunting of blood through the non-ventilated lung and impaired ventilation-perfusion matching in the ventilated lung have been proposed as mechanisms for the hypoxemia noted in these cases. The treatment of hypoxemia during OLV may include usual strategies such as the application of positive end-expiratory pressure (PEEP) to the ventilated lung and the application of CPAP to the non-ventilated lung. The use of PEEP in the ventilated lung is quick and easy to implement but may promote the shunting of blood to the non-ventilated lung and paradoxically worsen oxygenation. Providing CPAP to the non-ventilated lung reliably improves oxygenation. However the provision of even low levels of CPAP in the non-ventilated right lung is quickly detected by the surgeon who is viewing the field with magnified, stereoscopic vision. In fact, our surgeons prefer intermittent two-lung ventilation rather than the application of CPAP to the right lung. During periods of two-lung ventilation, the surgeon attends to other aspects of the operation, such as closure of groin incisions.

The insufflation of carbon dioxide (CO_2) into the right chest is commonly performed following deflation of the right lung. Insufflation of CO_2 into the chest reduces the amount of intracardiac air present at the conclusion of CPB and diminishes the likelihood of a surgical site fire. Hemodynamic compromise resulting from a tension

capnothorax is possible though we have encountered this complication only a few times [MJR1]in approximately 700 robotic mitral operations. Limiting pressure in the right hemithorax to 10 mmHg and insufflation rates below 2 to 3 L/min reduces the risk of a tension capnothorax is reduced.

One unique concern related to robotic MVR involves defibrillation. The small incision does not permit the performance of internal defibrillation, necessitating the use of external pads in a modified position because of the extent of the surgical field. The presence of a capnothorax further complicates the situation, since CO_2 acts as an electrical insulator, further hampering defibrillation efforts. If initial external defibrillation efforts prove unsuccessful, consideration should be given to resuming two-lung ventilation to reduce electrical impedance through the chest.

Line Placement and Bypass Cannulation

A minimally-invasive approach to cardiac surgery implies peripheral cannulation for CPB. However there are different CPB cannulation strategies, particularly for the venous return lines. Similarly, different strategies for cardioplegia delivery may be selected based on surgeon preference. Also, patient factors, such as significant aortic regurgitation, may necessitate the use of retrograde cardioplegia. Anesthesiologists may be tasked with placing lines both for venous drainage for cardiopulmonary bypass or cardioplegia administration. The location and number of such lines may, in turn, influence the selection of additional lines used for pressure monitoring, fluid administration, or drug delivery.

The primary method of venous drainage for CPB is placement of a cannula via the femoral vein that is typically advanced into the right atrium (RA) or superior vena cava (SVC). In addition, supplementary venous drainage may be accomplished by means of a cannula introduced into the right internal jugular vein (RIJ) and advanced into the SVC under TEE guidance. This SVC cannula may be placed entirely by the anesthesiologist with tubing passed around the surgical drapes to the CPB machine. Alternatively, a small, single-lumen cannula can be inserted by the anesthesiologist into the RIJ, close to the clavicle. This line is prepped into the surgical field. Later, under TEE guidance, the surgeon uses this cannula to introduce a guidewire, dilators, and finally a wire-reinforced venous cannula (Figures 2a, 2b). Supplementary venous drainage may also be provided by a commercially-available endo-pulmonary vent. This balloon tipped catheter has a design similar to a short pulmonary artery catheter and is inserted into the RIJ by mean of an introducer sheath. The tip of the endo-pulmonary vent is advanced with TEE guidance to a position in the main pulmonary artery, within a few centimeters of the pulmonary artery bifurcation and then connected by vacuum-assisted drainage into the CPB circuit.

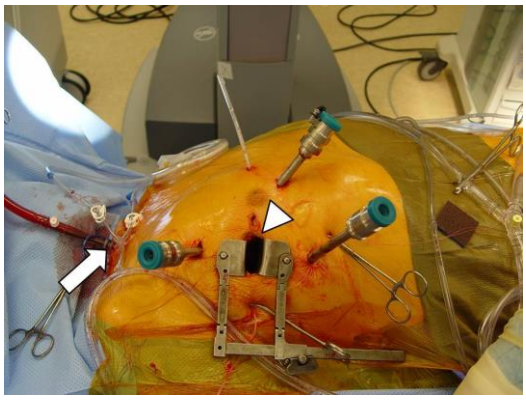

Figure 2a

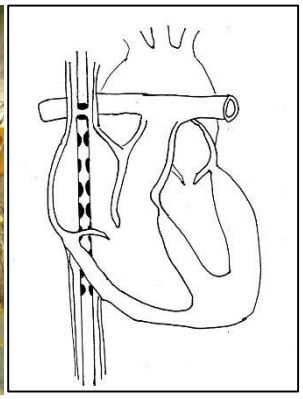

Figure 2b

Figure 2a. Surgical site photograph taken from the patient's right side showing the main surgical incision (arrowhead) as well as the SVC cannula (arrow) that has been placed by re-wiring a right IJ catheter.

Figure 2b. Sketch of one venous cannulation strategy that includes both a cannula introduced from the femoral vein and second cannula introduced via the right IJ.

Besides the small line that is prepped into the surgical field, we typically place a second line into the RIJ at a position that allows placement of surgical drapes between the two. This second catheter is the primary drug infusion and central venous pressure monitoring. The exact type of central venous line placed depends on the

preference of the anesthesiologist. We do not use a pulmonary artery catheter for robotic MVR cases. If an endo-pulmonary vent is used, pulmonary artery pressures can be transduced prior to CPB though once protamine is given, the endo-pulmonary vent is removed.

The RIJ may also be used to place a percutaneous coronary sinus catheter for retrograde cardioplegia delivery. Retrograde cardioplegia may be chosen as the sole method of cardiac arrest by choice or because of patient factors (significant aortic regurgitation). TEE, fluoroscopy, or both methods may be used to confirm correct catheter position in the coronary sinus.

Arterial pressure monitoring is accomplished by means of a left radial artery catheter. The left radial artery is preferentially chosen because the right arm is positioned along the patient's right side in front of the bedside surgeon and difficult to access during the case. However if endo-aortic balloon occlusion of the ascending aorta with antegrade cardioplegia is planned, then bilateral radial arterial catheters are placed. Damping of the right radial arterial pressure waveform is presumed to represent migration of the endo-aortic balloon with innominate artery occlusion and should prompt examination of endo-aortic balloon position with TEE. Alternatively, intraoperative cerebral oximetry has also been suggested as a means to detect endo-aortic balloon migration and innominate artery occlusion.

Transesophageal Echocardiography

The practice of robot-assisted MVR depends heavily on intraoperative TEE. Besides diagnosis of mitral pathology and evaluation of the surgical repair, TEE is used to detect additional findings that may impact the conduct of the operation. The presence of more than mild aortic regurgitation may necessitate the administration of retrograde cardioplegia. Atrial level shunts may complicate passage of femoral venous guidewires and cannulae.

The need for real-time guidance during placement of guidewires and cannulae represents a unique role for TEE during robotic and minimally-invasive cardiac surgery. During cannulation of the femoral artery, continuous TEE imaging ensures that guidewire passage into the descending aorta has been successful, though the arterial cannula itself is not seen. When the endo-aortic balloon occlusion system is used, TEE is further used to verify final endo-aortic balloon position approximately 2 cm above the aortic root. Passage of a guidewire from the femoral vein is also monitored with TEE. Ideally the guidewire will pass through the RA and with the tip residing in the SVC. Occasionally the femoral venous guidewire is malpositioned across a patent foramen ovale or becomes coiled in the RA appendage. The position of the guidewire and venous cannula introduced into the SVC from the RIJ are also monitored. If percutaneous coronary sinus cannulation and placement of an endo-pulmonary vent are planned, TEE is also invaluable in confirming the positions of these devices as well.

Conclusion

The robotic approach to MVR offers significant benefits to patients in need of mitral surgery. The unique aspects of this practice create both challenges and opportunities for the anesthesiologists who participate in these operations.

ANESTHESIOLOGY 2017
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2D/3D Imaging: What Views are Best for Decision-Making

Sasha K. Shillcutt, MD, MS, FASE **Omaha, NE**
Associate Professor
University of Nebraska Medical Center

Lecture Objective: Identify the most valuable TEE views for assessing mitral anatomy for mitral repair with different surgical and percutaneous approaches.

There is a superb primer on the intraoperative TEE imaging of the mitral valve (MV) for repair by Mahmood and Maytal (see references). I recommend it as an in-depth resource on the MV. This short review will focus on views that are helpful in assessment of MV repair, and highlight structures to assess in both open and percutaneous MV procedures.

The bileaflet MV is a complex structure that is in continuity and structurally a part of the left ventricle. The MV can have an array of dysfunction: annular dilation, prolapse, restriction, flail, masses, and destruction. The MV should be interrogated from multiple anatomical planes in detail before and after any intervention. The key to imaging the MV is to have a standard, routine exam sequence in the OR that can be done with efficiency. While advanced quantification of the MV can be done off line, during the time constraints of the operating theater evaluation should include:

- Two-dimensional imaging with unlimited flexions and rotations
- Multiple probe depths and planes including simultaneous multiplane mode (0-180°)
- Color Doppler
- Spectral Doppler
- +/-3D imaging

TEE Views for Assessment of Mitral Valve Repair

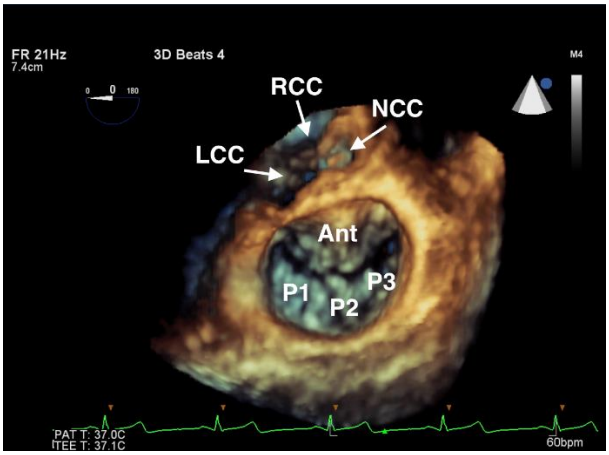
Table 1.

	Open Mitral Valve Repair	
	TEE View	*Structures to Assess*
2D	Midesophageal 4C	A3A2/P2P1, annular dimensions, tenting, coaptation dimensions
	Midesophageal Mitral Commissural	P3/A3A2A1/P1
	Midesophageal 2C	P3/A3A2A, pulmonary vein Doppler assessments
	Midesophageal LAX	P2/A2, post repair SAM
	TG Short Axis at level of Base	Assessment of stenosis, rheumatic disease
3D	Midesophageal LAX Zoom	Clefts and indentions, post repair leaks
	Midesophageal LAX Full Volume	Annular shape and dilation
	MV as viewed from the LA	Origination of jets, CFD
	MV as viewed from the LV	Abnormal leaflet motion: tethering/redundant leaflets
	Percutaneous Mitral Valve Repair Considerations	
2D	Midesophageal AVSAX	Transseptal puncture, posterior, tenting, 3-4cm above leaflets
	Midesophageal Bicaval	Transseptal puncture, posterior fossa & superior direction
	Midesophageal 4C	Coaptation depth & Length (<11mm,>2mm), flail gap (<10mm), device capture, post repair gradient (<5mmHg)
	Midesophageal Mitral Commissural	Correct Medial-Lateral Capture in MitraClip
	Midesophageal 2C	Transseptal Wire guidance into Pulmonary Vein/LAA
	Midesophageal LAX	Correct Posterior-Anterior Capture, Post-repair Evaluation
3D	Midesophageal LAX Zoom & Inter-commissural views	En face view of clip approaching leaflets , grasp and check that the device is perpendicular to the line of coaptation

According to guidelines by the American Society of Echocardiography by Lang et al, three-dimensional imaging of the MV "is recommended" for use in clinical practice in the following arenas based on literature:

- MV anatomy and stenosis assessment
- Guidance of transcatheter procedures (such as the MitraClip, mitral valvuloplasty, paravalvular leak closure)
- Important:
    - Midesophageal LAX is the most horizontal plane of the annulus; important for prolapse assessment and for the MitraClip to check that the device is perpendicular to the line of coaptation
    - Zone of leaflet coaptation should be approximately 1cmand predicts post-repair recurrence of mitral regurgitation associated with 5-year survival.

3D of the Mitral Valve: The surgical view



3D of the Mitral Valves as viewed from the Left Atrium aka "Surgeons View", as if the surgeon was standing on the right side of the patient and opens LA

- Aortic Valve: 12 o'clock position
- Mitral Valve: Anterior 12 o'clock position

How to get the 3D en face view of the MV:

1. Use biplane views to center MV annulus
2. Rotate Left - LA enface view
3. Rotate 30° to place AV at 12 o'clock
    a. View from LA side
    b. Rotate 180° to view from ventricular side

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Ischemic Mitral Regurgitation: surgical repair versus surgical replacement?

Douglas C. Shook, MD, FASE **Boston, MA**
Brigham and Women's Hosptial

Introduction
Mitral regurgitation (MR) is divided into primary and secondary etiologies. Primary (degenerative) mitral regurgitation is characterized by abnormal mitral valve leaflets with subsequent leaflet dysfunction/regurgitation. Secondary (functional) mitral regurgitation results from myocardial dysfunction and its subsequent impact on leaflet motion and coaptation. Ischemic MR is a subset of secondary (functional) MR where the progressive left ventricular remodeling and dilation is caused by myocardial injury. Simply put in primary MR leaflets are abnormal (myxomatous) and in secondary MR leaflets are normal but the ventricle and/or annulus is abnormal. Ischemic MR is when the abnormal ventricle is caused by either acute and/or chronic ischemia.

Mechanism and Evaluation of Ischemic MR
The MV annulus, leaflets, chordae, papillary muscles, and left ventricle must all be thoroughly evaluated to define the pathophysiology/mechanism of ischemic MR (Figure 1). The echocardiographic evaluation of ischemic MR must be just as rigorous as it is for other forms of mitral regurgitation. 2D and 3D echocardiography are uniquely suited to help define this complex interrelationship. Mechanisms of ischemic MR include reduced annular excursion during systole and annular dilatation, especially in the anterior/posterior dimension. Mitral valve leaflet motion is typically restricted or tethered. The restriction can be asymmetrical affecting the inferior-medial MV more commonly or symmetric typically in patients with multiple myocardial infractions (Table 1). The ischemic left ventricle often dilates becoming more spherical putting tension on secondary chordae producing a tenting effect on the MV leaflets. Papillary muscle dysfunction further complicates the pathophysiology and contributes to malcoaptation of the MV leaflets. Echocardiography must evaluate each of these mechanisms to define the reason for mitral regurgitation and potential interventions.

Repair or Replace
Current valve guidelines suggest surgical intervention in patients with severe ischemic MR who are symptomatic despite optimal medical heart failure therapy. The conundrum is whether to repair to replace the mitral valve. Several studies have reported that mitral valve repair should be performed with an undersized, complete, annuloplasty ring and mitral replacement performed utilizing a chordal-sparing technique. The first prospective, randomized controlled trial comparing MV repair with an annuloplasty ring versus chordal-sparing mitral valve replacement was reported by the Cardiothoracic Surgical Trials Network (CSTN). Two hundred fifty-one patients with severe ischemic MR were randomized to either repair or replacement. The primary endpoint was left ventricular end-systolic volume index, a marker of reverse remodeling. At 1 and 2-year follow-up, there was no statistical difference between the two groups regarding the primary endpoint or mortality (study was not powered for mortality). Patients in the repair group had more serious adverse events related to heart failure and cardiovascular readmissions. The repair patients also had higher rates of recurrence of moderate to severe MR at 2 years (58.5% versus 3.8%). The lack of durability in the repair population is likely because ischemic MR is not just annular dilation but also distortion of the subvalvular apparatus and ventricle. Mitral annuloplasty doesn't address this important mechanism of ischemic MR. In fact, an undersized annuloplasty ring may exacerbate leaflet restriction/tethering by displacing the posterior annulus farther away from the papillary muscles. Subgroup analysis of the CSTN trial found recurrence after repair was largely due to untreated leaflet tethering. Even mild MR after repair has been associated with adverse clinical outcomes, including death.

A question raised from the CSTN trail is could patients randomized to the repair arm be risk stratified for MR recurrence. The strongest predictor of recurrence after repair was the presence of a ventricular basal aneurysm and/or dyskinesis. This was observed in 62.1% of patients with recurrent moderate or greater MR versus 20.5% in those with no or mild MR. Other reported markers that help predict MR recurrence after repair and subsequent adverse left ventricular remodeling are listed in Figure 2. These predictors were not considered during randomization in the CSTN trial. More than 95% of trial patients with recurrent MR after repair had interpapillary

distances of more than 20mm, which is a marker for repair failure. It is likely that many of the patients in the repair group of the CSTN trial were at significant risk for MR recurrence based on the known predictors and should have been offered MVR instead.

Current Guidelines

The 2016 American Association of Thoracic Surgeons (AATS) Guidelines for Ischemic MR and the 2017 American Heart Association/American College of Cardiology Focused Update of the 2014 Valve Heart Guidelines have been published in the past year. Both guidelines have incorporated the most recent studies into their updates but do have some wording differences when compared closely (Table 2).

Summary and Conclusions

Indications for mitral valve surgery for moderate or severe ischemic MR are more limited compared to primary MR. Studies have shown that valve intervention for this patient group may improve symptoms and quality of life, but they have not improved overall survival. Surgical intervention for moderate ischemic MR **may be considered (benefit ≥ risk)** at the time of other cardiac surgery (ex. CABG), although the benefit is uncertain. Surgical intervention (repair or replacement) for severe ischemic MR is **reasonable (benefit>>risk)** at the time of other cardiac surgery and can be **considered (benefit ≥ risk)** as an isolated procedure for patients with advanced New York Heart Association functional class and have failed guideline directed medical therapy and cardiac resynchronization when indicated.

The decision to repair or replace the mitral valve is based on the most current published evidence and expertise of the surgeon, echocardiographer, and heart team. In severely symptomatic patients is **reasonable (benefit>>risk)** to choose chordal-sparing mitral valve replacement over a down-sized annuloplasty ring repair. In appropriate patients with severe, symptomatic, ischemic MR (no basal aneurysm/dyskinesis, no significant leaflet tethering, no significant LV dilation) an undersized annuloplasty ring may be **considered (benefit ≥ risk).** Incorporation of more advanced repair techniques (ex. papillary muscle sling) that address the leaflets and subvalvular apparatus might improve upon published results, but this remains to be determined by prospective trials.

Figure 1: Mechanisms of Ischemic Mitral Regurgitation

Annulus
- Diminished systolic excursion
- Dilatation (Anterior/Posterior > Commissural)

Papillary Muscle/Chordae
- Rupture (partial or complete)
- Elongation of the papillary muscle (can produce MV prolapse)
- Scarring/Retraction (MV leaflet restriction)

Ventricle (typically causes MV leaflet restriction)
- Global and focal aneurysmal dilatation
- Systolic regional and global dysfunction

Figure 2: Echo Predictors of Repair Failure

Annulus
- Annular diameter > 3.7cm

Leaflets
- Tenting height (mid systole) > 10mm
- Tenting area (mid systole) > 2.5cm^2
- Distal anterior leaflet angle > 25°
- Posterior leaflet angle ≥ 45°

Left Ventricle
- Basal aneurysm/dyskinesis
- Interpapillary muscle distance (tip to tip at end systole) > 20mm
- Left ventricular end-systolic diameter > 51mm
- Left ventricular end-diastolic diamter > 65mm
- End systolic volume ≥ 145mL
- Systolic sphericity index ≥ 0.7
- Wall motion score index ≥ 1.5

Table 1: Characteristics of Ischemic MR

Method	Asymmetric	Symmetric
Etiology	Inf/Post MI	Multiple Infarctions
Tethering	Post leaflet	Both leaflets
Tenting	Increased	Markedly Increased
Annulus	May be dilated	Dilated, flattened
Remodeling	Localized	Global
MR Jet	Posterioly directed	Central

Table 2: Current Valve Guidelines for Ischemic Mitral Regurgitation

2016 AATS Guidelines: Ischemic MR	2017 AHA/ACC Focused Update
Severe Ischemic MR	
See below	Mitral valve surgery is **reasonable** for patients with chronic severe secondary MR (stages C and D) who are undergoing CABG or AVR. **(COR IIa, LOE C)**
MV replacement is **reasonable** in patients with severe Ischemic MR who remain symptomatic despite guideline directed medial and cardiac device therapy, and who have a basal aneurysm/dyskinesis, significant leaflet tethering, and/or severe LV dilatation (EDD > 6.5 cm) **(COR IIa, LOE B)**	Mitral valve repair or replacement may be **considered** for severely symptomatic patients (NYHA class III to IV) with chronic severe secondary MR (stage D) who have persistent symptoms despite optimal GDMT for HF. **(COR IIb, LOE B)**
MV repair with an undersized complete rigid annuloplasty ring may be **considered** in patient with severe IMR who remain symptomatic despite guideline directed medical and cardiac device therapy and who do not have a basal aneurysm/dyskinesis, significant leaflet tethering, or severe LV enlargement **(COR IIb, LOE B)**	It is **reasonable** to choose chordal-sparing MVR over downsized annuloplasty repair if operation is considered for severely symptomatic patients (NYHA class III to IV) with chronic severe ischemic MR (stage D) and persistent symptoms despite GDMT for HF. **(COR IIa, LOE B-R)**
Moderate Ischemic MR	
In patients with moderate IMR undergoing CABG, MV repair with an undersized complete rigid annuloplasty ring may be **considered (COR IIb, LOE B)**	In patients with chronic, moderate, ischemic MR (stage B) undergoing CABG, the usefulness of mitral valve repair is uncertain. **(COR IIb, LOE B-R)**

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Risk Reduction and Safety Improvements from New Vascular Access Technologies

Franklin Chiao **New York, NY**

Background
Establishing vascular access is a procedure critical to safe medical care. Clinicians sometimes know little about the vessel characteristics aside from anecdotal reports and experiences despite the fact that there is currently some literature about the number of veins visible in patients or the patient characteristics associated with difficult vascular access. Vascular access technology is a major help in cannulating vessels. Many providers do not have experience using these technologies to access vessels. Ultrasound and infrared are two of several new technologies that are helpful in reducing risk of complications and liability, while improving safety(1)(2). This lecture is designed to increase safety and reduce risk by implementing new approaches and technology to obtain vascular access.

Risk for our session is referring to complications not only from failed vascular access, but also from the attempts themselves. It is measured by number of attempts, time to cannulation, failure rate, pain and more serious complications such as thrombosis, infection, hematoma, infiltration, and low patient satisfaction.

Some safety improvements include new catheter designs that have allowed for longer functional dwell time- this includes higher infusion rates, antibiotic coatings, etc. Midline catheters are included in this discussion. Ultrasound technology allows for the computerized measurement of catheter to vessel size. Catheter size to vessel size ratio is one of several important concepts to reduce thrombosis and infiltration. Risk Factors for infiltration are a vein/catheter ratio <2 and use of hyperosmotic solutions.

Lecture concepts
The learner will design a plan on how to reduce risk and improve safety for patients particularly with difficult vascular access. They will see the technologies available to enhance vessel visibility. The learner will identify the functions needed to enhance visualization of vessels under ultrasound guidance. The basic physics of ultrasound will be covered. There will be a demonstration of the common visual artifacts. The circling technique will be shown. The physics of infrared technology will be discussed. Safety principles for the operation of these devices will be examined. There will be a case discussion.

In addition, the learner will compare techniques and clinical applications of ultrasound-guided and infrared technology to improve success rate and reduce the risk of complications. They will establish a technique to handle ultrasound equipment while performing catheter placement. The learner will see different ultrasound equipment available. They will differentiate ultrasound images of vessels, nerves, fat, and muscles. They will participate in a discussion about methods of improving the ultrasound image, positioning the patient, the scanner, visualizing the catheter point and verifying the anatomy as the catheter is advanced.

Evidence-based Benefits/Risks of Technology
Benefits of technology include decreased complications, increased success rate, and decreased number of attempts(2). Economic benefits are significant. Tremendous labor and work hours are spent by nursing, physicians, and staff on accessing these veins, including the requirement of general anesthesia. The general anesthesia is a particular risk in children as per the FDA warning on neurotoxicity. General anesthesia is frequently used to place central lines in children. Risks of using the actual devices themselves are few as they do not emit radiation. Training and costs of purchasing machines are the main expenses.

Demographic Factors for High Yield Risk Reduction
Risk factors for difficult vascular access include obesity, younger age, darker skin, asian or black ethnicity(3). Scoring systems have also been developed as an aid to indicate when technology should be used.
The Difficult Intravenous Access(DIVA) scoring system is one example of this(4).

Vessel Size Ratio
This was discussed earlier, as one knows, the risk of thrombosis and catheter failure is higher when the catheter in the vessel impedes more of the vessel flow. It is sometimes safer to use multiple smaller catheters versus one or two large ones. There will be a list of the published flow rates. Evidently, three 22gauge catheters flow at about the same rate as one 18gauge, and two 22gauge catheters flow quicker than one 20gauge catheter.

Infrared Technology
Infrared technology has made a major impact in decreasing failure rate. One of the seminal studies showed the improvement in veins visible with the infrared. Chiao and colleagues examined 768 arms in a randomized prospective trial. Two additional veins were identified per arm across all demographic groups. The amount of additional veins seen increased with age(3).

Additional studies showed particular groups of patients that allowed for risk improvements. 115 neonates for PICC line were studied. The success odds ratio was 3.05 with infrared(5). Time to cannulation, success rate, attempt number were all improved in pediatric patients(6).

It was also helpful for phlebotomy as 165 difficult IV hemophiliac patients were studied. Difficult veins were fewer with infrared; 76% versus 92%. There was also less pain in the same number of attempts(7).

Ultrasound Technology
Ultrasound is the most studied and widely used for vascular access technology. In 60 patients who had three failed attempts and a history of difficult IV access, cannulation success was 97% versus 33%. Placement took 13 minutes versus 30 minutes. 1.7 punctures versus 3.7 punctures were required. Patient satisfaction was 8.7/10 versus 5.7/10(8).

In another study, 75 patients with difficult IV access and eventual ultrasound guided cannulation were examined. Median IV survival time was 26 hours and about half failed within 1 day mostly due to infiltration. Authors used a 6.3cm catheter which has a similar failure rate to shorter catheters. Only 5 patients needed central lines, so 42 patients were saved from a central line due to ultrasound success. No infections or thrombosis occurred.

For central line access, 431 patients with landmark placed central line versus 326 patients placed with ultrasound were studied. With ultrasound, 42% fewer punctures occurred and a 26% greater first attempt success was reached(9).

For arterial puncture, similar safety improvements occurred. 30 patients were studied and catheterization success was 100% in the ultrasound versus 80% in the palpation group. First attempt success was 67% versus 20%, 1.3 attempts versus 2, and a shorter time in the ultrasound versus landmark groups occurred respectively(10).

Needle probe tracking devices evidence is early and promising(11)(12).

Historical Technology
There is also some historical perspective as early techniques and technology focused on increasing engorgement. Esmarch bandage was used during the wartime period(13). Variations of this were applied(14). Rhys-Davies exsanguinator worked similarly(15)(16). Next, a vacuum device applied for 30 seconds to 100mmHg increased engorgement but at 60seconds, petechiae occurred(17). 21 patients were examined with a 90% success rate and mean venipuncture time was 38 seconds(18).

Transillumination is one of the more interesting technologies. With lights off in the room, and the device on the opposite side of the arm, light shines through and illuminates veins. It is helpful in infants, but risk of heat, discomfort, and burns is present(19)(20).

Doppler also is another safe and effective tool for vascular access. By squeezing the forearm and scanning for loudest sounds, veins can be found. Of 24 arms, 23 had the largest vein identified (21).

There is ongoing innovation in vascular access technology. The vein entry indicator device is one example. It measures change in pressure to indicate venous catheter placement(22). Veins threaded over a wire have also been introduced recently.

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ANESTHESIOLOGY 2017
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Radiologic Assessment: An Objective Tool to Assess Frailty

Itay Bentov **Seattle/WA**

"Man born of woman is of few days and full of trouble. He springs up like a flower and withers away; like a fleeting shadow, he does not endure." (Job 14:1-2)

The ageing population, and the syndrome of frailty.
The aged are at increased risk for most perioperative complications1. When Social Security was initiated in 1935, 6% of the U.S. population was older than 65 years. By 2010 that percentage had grown to 13% and by 2040 it is expected to be nearly 20% of the U.S. population. Of the 73 million surgical procedures performed in the U.S. in 2006, 28% were on patients older than 65 years2. Aging is often accompanied by adverse consequences: a decline in physical performance, reduced gait speed and mobility, impaired nutritional status, and disorders of cognition. Together, these changes describe the syndrome of frailty. Frailty predominantly affects older adults and predisposes individuals to disease and disability 3-5. The prevalence of frailty is estimated at 7-16% in community-dwelling older adults. Frailty is defined as a biologic syndrome of decreased reserve and resistance to stressors resulting from cumulative declines across multiple physiologic systems, which results in vulnerability to adverse outcomes. Frailty is different from disability (such as visual impairment) and comorbidity (such as heart failure) and is an independent predictor of mortality in community dwelling adults6. Furthermore, frail patients suffer from a higher likelihood of mortality, morbidity and complications after procedures in a variety of surgical fields independent of age and comorbid factors 7-14.

Frailty assessment tools
The most commonly used frailty assessment tools, examine physical frailty through assessment of physical function. Different tools vary in their inclusion of other factors such as cognition, disability, or comorbidity 15. These frailty assessment instruments combine direct measurement (walking speed, grip strength, clock drawing) and patient reported variables (history of weight loss, weakness or fatigue)16. Other tools assess "accumulation of deficits", for example symptoms (trouble with vision), disabilities (help in preparing meal) and disease classifications (high blood pressure, migraine, glaucoma), from a range of severity, from items associated with an increased risk of death (cancer, stroke) to those that typically cause more discomfort than disability (dexterity, vision problems)17. However , a clear consensus definition of frailty does not emerge from the literature18. A Delphi method based consensus project to define an operational definition of frailty could not reach agreement on the proposed diagnostic paths and procedures needed to achieve an operational definition. Nor on an objective measure such as biomarkers including inflammatory response C-reactive protein, interleukin 6, Tumor necrosis factor α , clinical parameters (hemoglobin, serum albumin), hormones (dehydro epiandrosterone sulfate, testosterone, insulin-like growth factor 1, vitamin D), products of oxidative damage (advanced glycation end products, protein carbonyls, oxidized low-density lipoproteins), antioxidants (carotenoids and α-tocopherol)19.

Sarcopenia and Osteopenia
Sarcopenia is defined by low muscle mass and impaired muscle function20. Loss of muscle fiber begins at approximately 50 years of age and by age 80 healthy individuals have lost about 30-50% of their muscle mass21. There is substantial variability between individuals in rates of sarcopenia that can be explained by gender, genetics and lifestyle; however, much of the variability among individuals remains unexplained. Several frailty assessment tools assess sarcopenia through attributes shared between sarcopenia and frailty, such as weight loss, weakness, and fatigue. Like frailty, the presence of sarcopenia has been linked to poor outcomes in various pathological conditions 22,23. Age-related osteopenia (bone mass loss that is less severe than osteoporosis) is considered a condition primarily affecting postmenopausal females; however, older males (as well as those treated by glucocorticoids or with androgen deprivation therapy for prostate cancer) are also at increased risk for osteopenia. Osteopenia is also related to frailty24-26. While frailty encompasses a wider band of physiologic problems than either sarcopenia or osteopenia the objective methods to measure sarcopenia or osteopenia may thus serve as a potential indicator of frailty.

Radiographic assessment of frailty

The gold standard for assessing sarcopenia is cross-sectional imaging; the best described method is relevant to the ambulatory setting: use of dual energy X-ray absorptiometry (DEXA)–a modality not suited for acute care practitioners in the operating rooms or the intensive care units20. However other radiological methods that can assess sarcopenia and osteopenia are often utilized by anesthesiologists:
computed tomography, as well as a a low-cost, low-risk, and portable tool that has become ubiquitous in anesthetic practice; the ultrasound.

Computed tomography assessment of sarcopenia and osteopenia

The most common areas are abdominal muscles at the lumbar levels, assessing either total muscle volume and density or specifically targeting the psoas muscle). Other muscles that were described are muscles of the thigh and paraspinous muscles. To measure osteopenia, the most common approach was via average HU calculation of a small region of interest over the cortical bone of the lumbar vertebral bodies. Image analysis procedures typically involved identification of the vertebral body using a sagittal cross-reference, then an axial view to measure bone density.

Ultrasonographic assessment of sarcopenia and osteopenia

Although several individual muscles and muscle groups have been evaluated, the commonest area of is the thigh. There were, however, many variations of thigh assessment: at the midpoint the mid-point of the anterior thigh as 50% of the distance between the lateral condyle of the femur and the greater trochanter and calculating the ratio between muscle thicknesses of the anterior thigh and posterior thigh. Some isolate specific muscles (rectus femoris, vastus intermedius) rather than measure the total muscle thickness of an anatomical compartment. Correlation of muscle echo intensity to function has also been assessed. Notable findings from some of these studies are the age-related decline in muscle thickness among community-dwelling adults27, and the correlation between muscle loss and functional measures28. Studies used quantitative ultrasound to identify osteopenia. However, all of these studies used specialized quantitative ultrasound devices, rather than general use portable ultrasound devices.

Can we do it?

Frailty assessment by radiologic modalities can detect muscle and bone loss which are associated with functional outcomes. Rectus femoris cross-sectional area in surgical ICU patients predicts short-term outcomes similarly to traditional frailty assessment tools29. A retrospective cohort study in our institution (a level I trauma center) in which we opportunistically assessed sarcopenia and/or osteopenia in total cross-sectional muscle area and bone density at the L3 vertebral level, in admission abdominopelvic CT scans from patients 65 years and older admitted to the intensive care unit and correlated it to one-year all-cause mortality(and30-day all-cause mortality, 30-day readmission, hospital length of stay, hospital cost, and discharge disposition).We found that among the those who survived to discharge, sarcopenia and osteopenia were associated with higher risks of 1-year mortality alone and in combination. After adjustment, the hazard ratio was 9.4 (95% CI, 1.2-75.4; P = .03) for sarcopenia and osteopenia, 10.3 (95% CI, 1.3-78.8; P = .03) for sarcopenia, and 11.9 (95% CI, 1.3-107.4; P = .03) for osteopenia30. More than half of older trauma patients in this study had sarcopenia, osteopenia, or both. Each factor was independently associated with increased 1-year mortality. Given the prevalent use of abdominopelvic CT in trauma centers, opportunistic screening for radiologic indicators of frailty provides an additional tool for early identification of older trauma patients at high risk for poor outcomes, with the potential for targeted interventions. This may translate to accurate frailty assessment in patients who may not otherwise be able to participate in functional testing, and avoids the need to rely on partial medical records or surrogate reports.

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ANESTHESIOLOGY 2017
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Basic Neurobiology of Depression

Name **Piyush Patel, MD** **San Diego, CA**

Depression is a clinical syndrome that is one of the major causes of increased morbidity and mortality. The currently available treatment regimens, while being effective in subsets of patients, often do not lead to remission and do not mitigate all of the adverse effects of depression. Despite intensive research effort, the underlying mechanisms of depression remain incompletely understood; a better understanding of these mechanisms is of fundamental importance to the development of novel therapeutic strategies. A number of mechanisms are operative in depression; these include monoamine-serotonergic dysfunction, loss of trophic factor support, stress induced hypothalamic-pituitary axis abnormalities, neuroinflammation and excitatory synaptic loss. In this brief review, the neurobiology of each of these mechanisms will be presented. For clinical application, the reader is referred to a companion manuscript authored by Laszlo Vutskits.

Monoamine Hypothesis

The monoamine hypothesis of depression originated from the observations that agents that reduced metabolism (MAO inhibitors) or uptake of monoamines (tricyclic agents) manifested efficacy in the treatment of depression and that the antihypertensive agent reserpine, which depletes catecholamines, produced depression. Currently available antidepressants affect primarily serotonin levels by reducing reuptake (SSRI) or metabolism (MAOI). Under normal conditions, serotonin acts on 5HT receptors in postsynaptic neurons and leads to increased phosphorylation of CREB (Figure 1) and increased synthesis and release of the trophic factor brain-derived neurotrophic factor (BDNF). BDNF in turn provides trophic support to surrounding neurons and increases their activity (for example, glutamate release). The uptake of serotonin is facilitated by SERT, a high affinity monoamine transporter (Figure 1). Increased activity of SERT in the setting of depression leads to a reduction in serotonin induced BDNF synthesis and reduced trophic factor support. Selective serotonin reuptake inhibitors (SSRI), which are the current mainstays in the treatment of depression, restore serotonin signaling by reducing the uptake of serotonin from the synaptic cleft into presynaptic neurons.

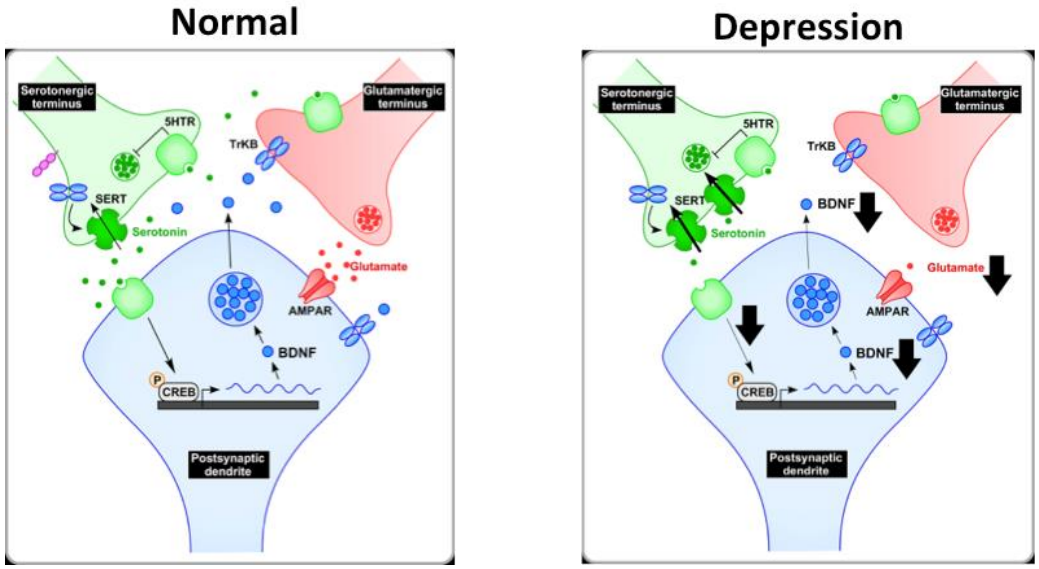

Fig 1.

There are a number of limitations of the serotonin hypothesis. SSRI increase serotonin levels in the brain rapidly yet the mood changes take considerably longer. SSRI are effective in only a small subset of patients, lead to remission in only about one third of patients, and are ineffective in many patients. Moreover, there is a loss of neurons in the dorsal raphe nucleus, the main serotonergic neurons in the brain, in some but not all patients. Krishnan and Nestler, 2008.

Neurotrophic and Neurogenesis Hypothesis

Neuronal circuitry is highly plastic in that neuronal connections can be strengthened or weakened in an activity dependent manner. Trophic factors, in particular BDNF, play vital roles in this plasticity. A number of stressors reduce BDNF levels and BDNF signaling. In addition, neurogenesis in the dentate gyrus is reduced by stress; it is increased by SSRI, exercise, environmental enrichment, ECT, lithium and by trophic factors. In pre-clinical studies, BDNF increases brain monoamine levels and produces an anti-depressant effect. SSRI increase BDNF and the loss of BDNF reduces SSRI efficacy. In humans, there is a loss of volume in the hippocampus and dendritic atrophy in the prefrontal cortex; these adverse effects are reduced to a certain extent by SSRI. In post mortem human brain tissue, a reduction in BDNF levels has been reported. In human patients with a single nucleotide polymorphism (BDNF Met-66), BDNF signaling is reduced. The presence of Met-66 has been associated with depression in males and in geriatric patients. Moreover, efficacy of SSRI is reduced in these patients. These data are consistent with the hypothesis that BDNF signaling plays an important role in major depression. However, it should be noted that BDNF levels are actually increased in the nucleus accumbens and that not all patients with Met-66 have depression. Indeed, Met-66 is associated with increased resistance to social stress. In aggregate, the available data suggest that BDNF plays an important role in depression but that other factors also contribute.

Neuroinflammation Hypothesis

There is substantial amount of evidence that links depression with a variety of inflammatory conditions. Infection induces a characteristic behavioral set, called sickness behavior, that is similar to the behavior of depressed patients. In the latter, increased levels of cytokines (such as IL-1, TNFa) have been documented, and interestingly, the administration of SSRI can reduce this cytokine level. In patients with chronic inflammatory diseases, depression is often a common occurrence. Activation of microglia can lead to a reduction in BDNF, thereby reducing neuroplasticity, and in neurogenesis. By contrast, chronic inflammation can also increase anti-inflammatory cytokine and BDNF production by microglia. Hence, both toxic and protective effects of microglia have been demonstrated, and the net result is likely to be a function of the extent of inflammation and the underlying susceptibility of the individual.

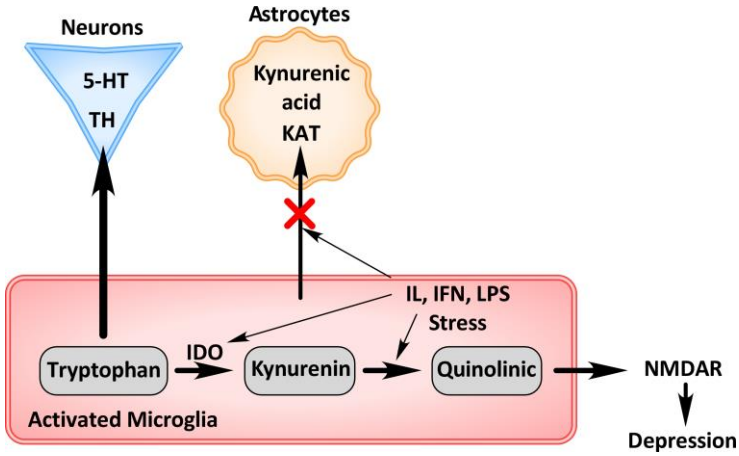

Fig 2

A specific pathway that may adversely impact glutamatergic signaling has been identified. In activated microglia, indolamine 2,3-dioxygenase (IDO), an enzyme that converts tryptophan into kynurenine, is upregulated (Figure 2). The result is synthesis of quinolinic acid and kynurenic acid in microglia, which by direct agonism of NMDA receptors, can produce depressive symptoms. Simultaneously, shunting of tryptophan into kynurenic acid synthesis reduces serotonin synthesis.

An interesting observation is that inflammation can increase SERT activity in the brain. By reducing serotonin levels in the synaptic cleft, depression behavior in increased.
Haase and Brown, 2015

Hypothalamic Pituitary Adrenal (HPA) Axis

The HPA axis is essential for the ability of the individual to manage stress. It is a closed loop system that is under negative feedback control (Figure 3). Corticotropin releasing hormone is released by the hypothalamus; CRH binds to CRH1 receptors in the pituitary gland and leads to the release of ACTH. ACTH causes release of cortisol from the adrenal gland. Cortisol, by action at the hypothalamus, reduces CRH release, thereby completing the feedback loop. Cortisol is a low affinity agonist at glucocorticoid receptors (GR) and a high affinity agonist at mineralocorticoid receptors (MR).

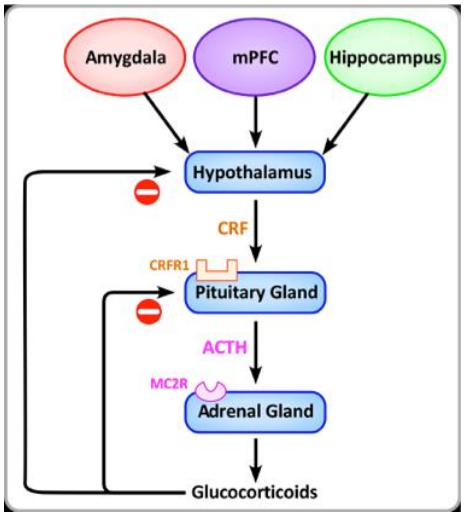

Fig 3

In major depression, particularly with delusion and psychotic features, the HPA axis is over-active, resulting in increased ACTH and cortisol levels. Negative feedback of cortisol at the hypothalamus is significantly reduced. The available data indicate that reduced negative feedback and excessive release of CRH contribute to hypercortisolemia in major depression. In small sample size studies, the administration of mifepristone, a progesterone receptor antagonist that at high doses also has GR antagonist activity, improved depressive and psychotic symptoms. However, in randomized trials, the drug did not find efficacy. Antagonists of CRH have also not shown to be of benefit in humans.

Rapid Antidepressant Action of Ketamine – Proposed Mechanisms

Ketamine is an NMDAR antagonist. The interest in the use of ketamine as a treatment in major depression was sparked by the demonstration that subanesthetic doses (0.5 mg/kg) produced a rapid anti-depressant effect. The effect was observed approximately 4h after its administration and lasted about 2 weeks; thereafter, depression symptoms returned. Repeated doses of ketamine can prolong the therapeutic effect beyond two weeks and this type of dosing is well tolerated by patients. Multiple randomized clinical trials and meta-anlayses have confirmed the robust anti-depressant effects of ketamine. Ketamine is most commonly available as a mixture of two enantiomers, R-ketamine and S-ketamine. S-ketamine has a higher affinity for the NMDAR and its anti-depressant effects have been confirmed; it is now approved for intra-nasal administration.

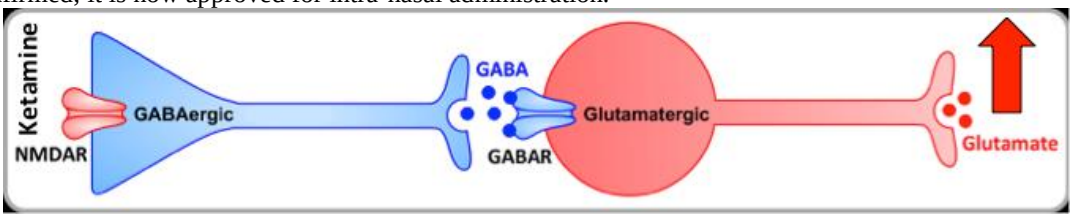

Fig 4

While anesthetic doses of ketamine suppress glutamatergic neurotransmission by NMDAR antagonism, sub-anesthetic doses lead to increased glutamatergic transmission by first suppressing interneurons, which by removing inhibition of pyramidal cells, leads to increased glutamate release and activation of *synaptic* NMDAR (Figure 4). Downstream signaling leads to inhibition of glycogen synthase kinase-3, activation of the mTOR pathway, increased BDNF and protein synthesis and synaptogenesis (Figure 5). Simultaneously, blockade of *extra-synaptic* NMDAR

relieves the inhibition of protein synthesis. Of interest is the demonstration that lithium also inhibits GSK3; preclinical data indicate that the simultaneous administration of ketamine and lithium may enhance efficacy.

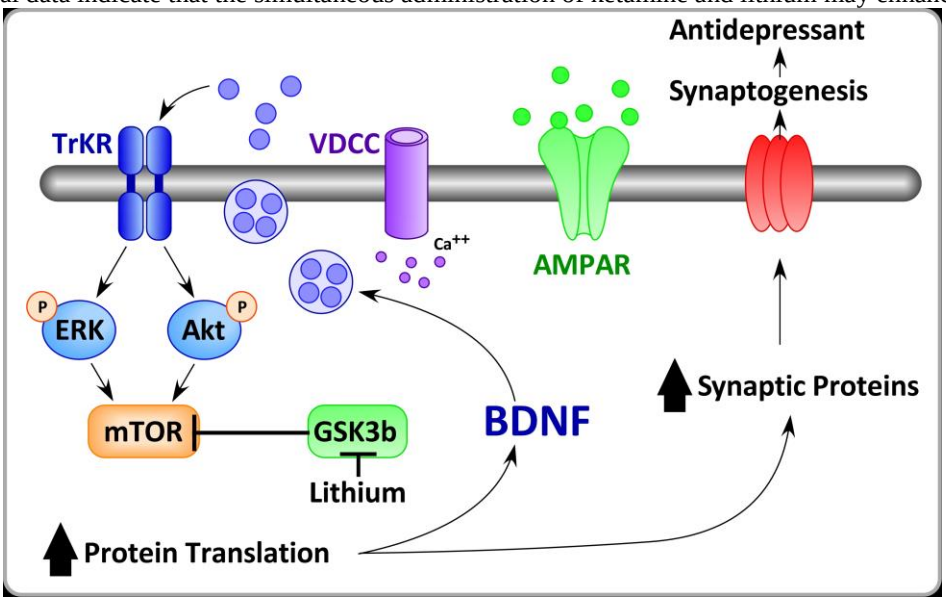

Fig 5
Ketamine induced increase in synaptogenesis persists for at least 7 days and the increased synapse number is accompanied by increased neuronal metabolism, especially in the medial prefrontal cortex. Ketamine also increases connectivity in neuronal circuits and increases the excitability of these circuits, not only in the prefrontal cortex, but also in motor and somatosensory networks.

Summary

Major depression is a complex disorder whose underlying mechanisms are incompletely understood. A number of hypotheses have been advanced; these include the monoamine, neurotrophic and neurogenesis, neuroinflammation, excitatory synapse and HPA dysfunction hypotheses. No single unifying hypothesis addresses the currently available preclinical and clinical data. It is therefore more likely that a number of abnormalities exist in patients with depression and that treatment should be tailored according to the underlying pathophysiology in each patient. It is therefore important to develop appropriate biomarkers to identify which patient will respond to a given treatment.

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Anesthetic-induced Modulation of Neuronal Plasticity: New Role for Anesthetics as Antidepressants

Name: Laszlo Vutskits, MD PhD **City/State :** Geneva, Switzerland

Introduction

Mental disorders are defined as mental or behavioural patterns causing either suffering or a poor ability to function in ordinary life (WHO, 2015). These conditions are generally characterized by a combination of abnormal thoughts, perceptions, emotions, behaviour and relationships with others. The burden of mental disorders continues to grow and the estimated global lifetime prevalence of these pathological states is estimated to reach over one third of the population worldwide with important regional differences (Kessler et al., 2000). In fact, while approximately 25% of Europeans present meeting criteria at some point in their life for DSM-IV-defined mental disorders, this prevalence is close to 50% in the United States (Kessler et al., 2005b; Wittchen and Jacobi, 2005). Anxiety and mood disorders are by far the leading causes of these pathologies in all continents followed by impulse-control and substance use disorders. Mental illnesses are the leading causes of disability-adjusted life years worldwide (Collins et al., 2011). According to the World Health Organization, the global cost of mental illness is estimated to exceed 2.5 trillion US dollars every year in the world and is projected to double during the next decade (Collins et al., 2011). Major depressive disorder is the leading cause of these expenses followed by direct and indirect costs linked to the management of schizophrenia (Collins et al., 2011). Understanding the pathophysiology of these diseases and thereby developing efficient therapeutic approaches is therefore of high priority public health importance.

General anesthetics comprise a family of largely heterogenous substances with the common capacity of rapidly inducing transient loss of consciousness and amnesia upon administration. Therefore, these drugs are indispensable components of the pharmacological armamentarium aimed to provide optimal surgical conditions, both for patients and surgeons, during the perioperative period. Given the seemingly on/off effects of general anesthetics on consciousness, it has been initially considered that exposure to these drugs does not induce long-term interference with central nervous system function. However, observations accumulating over the past few decades argue against this conception. It is now well established that general anesthetics are potent modulators of major neurotransmitter systems, and that even short-term pharmacological interference with neurotransmitter-driven neural activity patterns can have long-term consequences on brain physiology (Vutskits, 2012). This implies that general anesthetics cannot simply be acknowledged as drugs inducing a rapidly reversible state of unconsciousness but should also be granted as powerful, context-dependent modulators of neural plasticity. In this context, an intriguing possibility is that anesthetics-induced modulation of neural plasticity might represent a therapeutic value in the treatment of some psychiatric conditions. In line with this possibility, an increasing number of both experimental and clinical observations suggests a therapeutic role for general anesthetics in major depressive disorders. The present lecture is aimed to provide insights into this possibility.

Clinical trials suggesting a therapeutic role for anesthesia in patients with depressive disorders

In most cases, ECT is performed under general anesthesia. Since general anesthesia, in itself, is a robust modulator of brain states, an important question is to determine whether the therapeutic value of ECT is indeed linked to the passage of electrode-delivered electricity or to the impact of general anesthetics on neural networks. To elucidate this issue, active ECT should be compared with a stimulated procedure in which shocks are not delivered. Results from early studies aimed to address this problem were conflicting and open to important methodological criticism due to very low sample size and to the lack of adequate comparison groups. In 1953, Miller et al. have found a comparable improvement in social performance of 30 patients presenting chronic catatonic schizophrenia following treatment with either ECT, non convulsive stimulation under thiopental anesthesia or thiopental anesthesia alone (MILLER et al., 1953). Similar observations were made in a group of patients with mixed diagnoses of depressive states, where no statistically significant difference was found in outcome with straight ECT, ECT plus succinylcholine, ECT plus thiopentone, thiopentone alone and nitrous oxide anesthesia alone (BRILL et al., 1959). In contrast to these observations, another

study suggested a slight superiority of ECT compared to simulated ECT under thiopentone, but it is important to note that while 12 patients in this work received ECT only 4 subjects comprised the simulated group (McDonald et al., 1966).

Following these initial observational studies, randomized trials were set to compare anesthesia alone with ECT under anesthesia in terms of therapeutic efficacy. In a cohort of 32 patients suffering depressive psychosis, six brief unilateral ECT under methohexitone anesthesia over a period of two weeks showed comparable improvement on the Hamilton Rating Scale for Depression (HAMILTON, 1960) with a simulated procedure where study subjects received only anesthesia (Lambourn and Gill, 1978). In line with these observations, in a 6-months-long follow-up of 70 patients with severe depression, the Northwick Park Electroconvulsive Therapy trial demonstrated equivalent therapeutic value of 8 successive ECT sessions over a period of 4 weeks under thiopentone anesthesia when compared with a similar simulated ECT protocol where only thiopentone was administered (Johnstone et al., 1980). These trials thus brought convincing arguments in favour of the beneficial impact of general anesthesia in depressive states, and raised the intriguing possibility that anesthetics-induced decrease in neural activity might be an important component accounting for these effects. To further test this hypothesis, in two subsequent trials, Langer et al. demonstrated that 6 sessions of isoflurane anesthesia-induced brief burst suppression over 2 weeks had comparable effects with the delivery of 6 bitemporal ECT under general anesthesia in terms of both objective and subjective mood scales for up to 5 weeks (Langer et al., 1985; Langer et al., 1995). Importantly, the capacity for sustained concentration was significantly better in patients having received isoflurane compared to the ECT group (Langer et al., 1995). The antidepressant and neurocognitive effects of isoflurane anesthesia were subsequently reconfirmed in a group of 20 patients with medication-refractory depression (Weeks et al., 2013). In this study, ECT had modestly better effect at follow-up in severity-matched patients, while the isoflurane group showed better neurocognitive score improvement (Weeks et al., 2013). More recently, a prospective pilot study demonstrated anti-depressant properties of 50% nitrous oxide inhalation in patients with treatment resistant MDD(Nagele et al., 2015).

Rapid antidepressant effects of ketamine

A growing number of randomized clinical studies, accumulating over the past 15 years, suggests an antidepressant role for the competitive NMDA receptor antagonist ketamine in patients with mood disorders (Abdallah et al., 2015). It is interesting to note that the idea to use this particular anesthetics to treat depression is not based on the aforementioned putative link between the anesthesia component of ECT and the therapeutic effect. Rather, it stems from the so-called "initiation and adaptation" hypothesis assuming that the delayed effects of currently used classic pharmacological antidepressants are primarily due to the delayed adaptive effects of these drugs on glutamatergic neurotransmission systems, which stand in the center of the therapeutic response (Hyman and Nestler, 1996). In line with this postulate, preclinical studies demonstrate the prompt efficacy of NMDA antagonists in various animal models of depression (Trullas and Skolnick, 1990; Papp and Moryl, 1994). Further indications on the role of glutamatergic systems in the pathophysiology of depressive disorders came from human studies where proton magnetic resonance imaging revealed increased glutamate levels in the cerebral cortex of medication-free subjects with unipolar major depression when compared with a matched population of healthy controls (Sanacora et al., 2004). Last but no least, the glutamate release inhibitors lamotrigine and riluzole were found to exert antidepressant properties in clinical trials (Calabrese et al., 1999; Zarate et al., 2004). Altogether, these laboratory and clinical observations strongly suggest that drugs acting directly to decrease the efficacy of glutamatergic signaling are expected to demonstrate rapid onset of action to relieve symptoms in depressed patients.

Rapid therapeutic actions of ketamine were first demonstrated in a small group of 7 patients with major depression by Berman et al (Berman et al., 2000). In this randomized, double-blinded and placebo-controlled trial, intravenous administration of 0.5 mg/kg ketamine over a period of 40 minutes was associated with robust decreases in depressive symptoms , emerging progressively within 3 days. These initial observations were subsequently confirmed in a cohort of 18 patients with DMS-IV major depression, using an elegant cross-over design (Zarate et al., 2006). Compared to the placebo group, patients receiving ketamine showed significant improvement in depression as early as 2 hours following drug administration, and, most importantly, this effect remained significant for at least one week. These pioneering studies were followed by a large number of clinical trials, and several meta-analysis are now available supporting unanimously the therapeutic potential of ketamine in MDD both in drug free patients and in those who were under classic antidepressant medications (Caddy et al., 2014; Fond et al., 2014; Serafini et al., 2014; DeWilde et al.,

2015). Amongst the various symptom clusters characterizing MDD, ketamine appears to rapidly and robustly relieve anhedonia (i.e. the reduced capacity to experience pleasure), suggesting its action on the reward system in the brain (DeWilde et al., 2015). Relatedly, ketamine administration has been shown to rapidly reduce suicidal ideation, a feature that makes this drug uniquely suited to treat suicidal ideation in hospitalized patients (Price et al., 2009; DiazGranados et al., 2010). Importantly, administration of ketamine, 0.5 mg/kg over 40 minutes intravenously in the majority of trials, appeared safe with no life-threatening effects reported. Nevertheless, mild psychotomimetic symptoms, including unpleasant dissociative effects, were frequently reported but these were resolving rapidly following the end of administration. Transient hypertension and tachycardia were also reported but rarely required pharmacological intervention.

Conclusions and perspectives

Accumulating strong evidence indicates that some drugs can exert rapid therapeutic effects in MDD. While initial studies suggested therapeutic efficacy of several general anesthetics, particular attention over the past 10 years has been devoted to the NMDA receptor antagonist ketamine. This drug has been repeatedly shown rapid efficacy in depressive states and some of the mechanisms underlying this effect have been elucidated. Several important question, however, remain open. Amongst them, since the effects of single bolus ketamine appear transient, one important issue is to elucidate whether repeated injections of ketamine can maintain sustained remission in patients with MDD. While several case reports describe repeated ketamine injection with variable outcome, there is currently no study available to specifically address this question. Dose-response studies to determine the concentration-dependent effects of ketamine in MDD are also lacking. This line of research will be of utmost interest to determine the pharmacokinetic aspects of antidepressant properties. Identifying which particular modalities characterizing MDD are prone to positively respond to ketamine needs to be addressed in the future. In fact, new data suggest the efficacy of ketamine in rapidly reducing suicidality and in alleviating post-traumatic stress disorder symptoms (Feder et al., 2014; Price et al., 2014). Whether other psychiatric pathologies, such as obsessive-compulsive disorders or cocaine-dependence, can also be treated with ketamine is an intense field of current research (Bloch et al., 2012; Rodriguez et al., 2013; Dakwar et al., 2014). Last but not least, safety issues related to toxicity associated with repeated ketamine administration should definitely be elucidated especially in light of abuse liability to this drug(Morgan et al., 2012).

Although ketamine is emerging as the drug of choice to rapidly treat symptoms of MDD, we should definitely not forget the possibility that other general anesthetics could also exert similar effects. Indeed, early studies repeatedly revealed therapeutic effects of general anesthesia and this line of research should be actively pursued (Johnstone et al., 1980; Langer et al., 1985; Langer et al., 1995; Weeks et al., 2013). In line with these clinical data, laboratory observations also suggest that general anesthetics are powerful modulators of synaptic plasticity via the modulation of neurotransmitter release and growth factor signaling (Vutskits, 2012). Importantly, similar to ketamine, these drugs can rapidly induce the formation of new synapses (De Roo et al., 2009; Briner et al., 2010; Vutskits, 2012). It will, therefore, be important to determine whether or not, and in what dosing and administration regimens, currently used general anesthetics can have equivalent therapeutic efficacy in depressive states when compared to ketamine. Research in this direction will not only lead to an increased understanding of the effects of general anesthetics on the central nervous system, but might open new avenues for anesthesiology as a discipline to administer general anesthesia with a therapeutic goal to improve pathology in mood disorders and, potentially, in other psychopathologies.

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ANESTHESIOLOGY 2017
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Sepsis: Current Concepts and Perioperative Management

Mark E. Nunnally, M.D., FCCM **New York, New York**

Introduction

Sepsis is a high mortality syndrome and substantial health burden. In the U.S., about 250,000 people die of sepsis annually, killing more people than breast cancer, prostate cancer and AIDS combined (1). It is a comorbidity complicating many major surgeries, and is often responsible for an "emergency" designation. The increased morbidity and mortality of emergency status patients can be partially attributed to sepsis physiology. In one study, 40% of perioperative cardiac arrests were associated with sepsis, and these had a 77% mortality (BMJ chapter ref 7).

Sepsis also entails a re-tuning of the body's metabolic, inflammatory, neurologic and endocrine systems to coordinate a systemic response in every organ system. A new consensus definition of sepsis defines it as a dysregulated response to infection." (2) A maladaptive response causes changes in physiology whose purpose is not completely understood. Some adaptations, such as a loss of systemic vascular tone, can be detrimental. Conversion to a more stable but maladaptive chronic critical illness state is more ominous, and is a risk when control of sepsis is delayed.

In an era of powerful antibiotics and a better understanding of how to use them, the primacy of sepsis should confuse us as clinicians. Our patients are dying of the same illness (infection) that other patients did 100 years ago. The details are different, but sepsis still persists and perseveres. In recognition of this intractable problem, basic science research, translational clinical trials and guidelines production continue at a fast pace.

Mastering the care of sepsis involves understanding several important concepts. Sepsis is a spectrum of disease requiring aggressive and timely management. Effective management is based on controlling the source of infection and managing the body's common responses to severe illness. It entails taking corrective actions before the patient's physiology transitions from an acute to a chronic critical illness state. Finally, sepsis is ideal for examining the way clinical care is delivered and directed at institutional, societal and governmental levels.

The sepsis syndrome: common themes

Sepsis has been defined by a loose set of criteria (3), among which are signs of inflammation linked to infection. Another system for describing the syndrome is the PIRO model (predisposition, infection, response, and organ dysfunction) (4). The criteria for defining and characterizing sepsis are nonspecific. For example, urosepsis is clinically different from sepsis with influenza, even though many factors are common to both.

The traditional definition of sepsis combined the systemic inflammatory response syndrome criteria with a suspected or known infection (5). *Severe sepsis* was defined as sepsis plus evidence of organ dysfunction. *Septic shock* was sepsis with hypotension unresponsive to fluid loading. These definitions, although helpful in describing the disease state for research and discussion, lack accuracy. The SIRS criteria are nonspecific. Worse, they miss a significant number of patients that go on to manifest sepsis (6). The definitions of sepsis have now been changed to reflect a dysregulated response to infection, manifest by organ dysfunction measured as a 2 point or greater increase in the Sequential [sepsis-related] Organ Failure Assessment (SOFA) score (Table) (2). Efforts to distinguish types of sepsis (e.g., by anatomic site or organism) in ways that impact prognosis and therapies are ongoing.

Table: Broad diagnostic criteria for sepsis (Modified from references 2 and 3):

Infection:	documented or suspected
General variables:	T > 38.3 or < 36°C, HR > 90/min, ↑ RR, encephalopathy, edema or positive fluid balance, hyperglycemia

Inflammatory variables:	WBC > 12,000 or < 4000/mcL, > 10% immature forms, ↑ C-reactive protein, procalcitonin
Hemodynamic variables:	SBP < 90, MAP < 70 mmHg or a decrease > 40 mmHg, SvO_2 > 70%, Cardiac Index > 3.5 L/min
Organ dysfunction variables:	hypoxemia, oliguria, ↑ creatinine, coagulopathy, ileus, ↓ platelet count, ↑ bilirubin
Tissue perfusion variables:	↑ lactate, ↓ capillary refill, mottling
Sepsis-related Organ Failure Assessment (SOFA) score:	PaO_2/FiO_2, Glasgow coma score, mean arterial pressure or administration of vasopressors required, bilirubin, platelet count, creatinine or urine output as markers of end-organ dysfunction
[Sepsis-related] SOFA (qSOFA)	Respiratory rate ≥22/min, altered mentation, systolic blood pressure ≤100 mmHg

Central to sepsis is inflammation. Systemic responses to infection range from elevated white blood cell counts to fever, hyperglycemia, and changes in intercellular mediators. Inflammation has been the main focus of sepsis research for over 40 years. Patients don't usually die from inflammation, however; they die from organ dysfunction.

Organ dysfunction in sepsis takes many forms and affects every organ system. Renal (e.g., acute kidney injury), vascular (vasoplegic shock) and respiratory failure (acute lung injury/acute respiratory distress syndrome) are well recognized sequelae of severe sepsis, but endocrine (hyperglycemia), neurologic (encephalopathy), and gastrointestinal (ileus) dysfunctions often presage severe sepsis and are signals to intervene before the syndrome worsens.

The cardiovascular effects of sepsis most directly affect anesthetic management, but clinicians should be aware of other risks, including electrolyte abnormalities, elevated aspiration risks, gas exchange abnormalities, and increased sensitivity to anesthetic agents. Cardiovascular changes include a loss of arterial tone (vasoplegia), capillary leak syndrome, venous pooling of blood, and ventricular dysfunction. Typically, a patient presenting with sepsis and hypotension will respond favorably to fluid resuscitation, and guidelines recommend volume challenges on the order of 30 mL/kg crystalloid (7). However, the detrimental effects of tissue edema, especially on oxygenation, may limit resuscitation. A subset of septic patients demonstrates right heart dysfunction, and aggressive volume resuscitation in these patients might worsen their shock rather than improve it. For these reasons, a rational approach to volume resuscitation combines a pragmatic early intervention of volume resuscitation with boluses of crystalloid with enhanced monitoring to define endpoints of volume administration. Such monitoring ideally includes dynamic measures of fluid responsiveness (e.g., pulse pressure variation, hemodynamic response to straight leg raise). Many patients in septic shock will require pressors. Data such as lactate clearance, pulse pressure variation while on positive pressure ventilation and central or serial mixed venous oxygen saturation measurement can help determine response to volume and define clinical criteria for vasoconstrictor administration to improve a still insufficient circulation. Inotropic support is only recommended in situations where impaired contractility is a suspected contributor to shock, and echocardiographic evidence is the most helpful approach to making this distinction. Recommended pressors include norepinephrine (first line), epinephrine (secondary) and vasopressin (adjunct). In any special circumstance (e.g., high suspicion of right ventricular failure, nonresponse to therapy), additional monitoring, such as a pulmonary artery catheter or echocardiogram may be helpful. Finally, in the setting of shock refractory to even pressors, empiric steroid administration (e.g., hydrocortisone, 50 mg IV every 6 hours) is indicated. In this circumstance, clinicians may elect to sample plasma for cortisol levels. Data do not support steroids for patients in sepsis without shock (8).

Another characteristic of the pathogenesis of sepsis is energy failure. Defects at the level of the mitochondria alter cells' ability to generate energy. These failures can predict mortality (9). Patients with ineffective aerobic respiration tend to be the ones who die. Conversely, the early sepsis response is associated with hypermetabolism. Although mixed venous or central venous oxygen saturation monitoring may help determine patients for whom metabolism outstrips oxygen supply, energy failure may raise central venous oxygen saturations through decreased consumption. Historically, evidence supported an "oxygen debt" of early sepsis, corrected with red cells and inotropes (10). A curve of supply-dependent oxygen consumption suggested many patients required enhanced oxygen delivery. This finding has not been replicated, and many now believe it to be an artifact of invasive hemodynamic measurements. Repeat studies using calorimetry do not replicate the supply dependency (11). Providing "supra-normal" levels of oxygen delivery above those needed to raise central venous saturation and indices of organ perfusion is no longer recommended (7).

Histologically, a characteristic of the septic response is apoptosis, or programmed cell death. Most commonly, this is expressed in populations of lymphocytes (12). Why immune cells would selectively die off in the throes of systemic infection is a mystery. Immune dysfunction is a classic finding in sepsis, and many septic patients suffer secondary infections. Organisms like vancomycin-resistant *Enterococcus* species, *Acinetobacter baumannii*, and *Cytomegalovirus* (13, 14) afflict septic patients more than healthy ones, likely because of immune dysfunction. This, combined with coagulation abnormalities (inflammation and coagulation are linked) and elevated risk of thromboembolic disease, mean that septic patients are at heightened risk of complications.

Over time, and with worsening injury, patient physiology changes. Endocrine exhaustion manifests as a loss of hormonal pulsatility and decreased levels of secretagogues and end hormones (15). Vital signs and physiologic rhythms stabilize (an unhealthy response), the results of defective autonomic signaling. Delirium may transition to functional cognitive deficits. Survivors of this syndrome have poor functional outcomes, but many do not survive.

Why do patients become septic?

Infection drives the septic response, yet many systemic changes during the sepsis syndrome are common to noninfectious causes of inflammatory responses. Components of SIRS are conserved across animal species, and in multiple animal models these components protect an organism from ongoing damage and allow it to heal. A complicated network of signals and activities that correct derangements and repair damage results in an overlap of inflammation, coagulation, metabolism, immunologic function, neurologic function, and tissue growth systems. The syndrome is fundamentally adaptive. In a case of sepsis, these responses are appropriate, but are dysregulated, and may be detrimental. Historically, many patients would not survive the initial insults of the sepsis syndrome. With intensive care, patients survive these previously fatal insults, but survive to suffer the natural history of prolonged sepsis physiology. Modern critically ill patients are unique and their illness has progressed to physiology that would never be seen in "the wild." In later phases (i.e., chronic critical illness) dysfunction becomes prominent. It is in these later phases when many patients die.

Sepsis management: key interventions

The Surviving Sepsis Campaign, first launched in 2002, details the evidence in support of sepsis therapy, translating the large body of sepsis literature into guidelines (7). Timely diagnosis, antibiotic therapy and goal-directed fluid resuscitation are key components of sepsis management. Several of the suggestions and recommendations directly influence management in the operating room. The anesthesia care team contributes to care by managing shock resuscitation. This is facilitated with physiologic goals such as mixed-venous oxygen saturation and lactate clearance. They confirm diagnoses by drawing blood, urine and sputum cultures. Finally, by facilitating the timely administration of antibiotics (ideally after cultures are drawn, but as quickly as possible), the team can have a positive impact on patient mortality. Anesthesiology-based expertise in monitoring and procedures can facilitate timely and effective care. Central venous and arterial access helps with resuscitation and management. Support of failing organs is ideally suited to anesthesiologists and should be viewed as akin to management in the intensive care unit. With surgical sepsis, the locale of the intervention (intensive care unit versus operating room) should make no difference in the goals of resuscitation and antibiotic therapy. Facilitating source control through timely surgical intervention, however, can make a major difference in outcomes.

What sort of a difference can these interventions have? Absolute mortality from sepsis decreased more than 6% as compliance with Surviving Sepsis Campaign recommendation bundles increased (16). Curiously, compliance in this study increased from 18.4 to 36.1%, suggesting that the recommendations are neither easily nor frequently adopted. Both evidence and rationale support timely intervention. Anesthesiologists can and should strive to facilitate cultures, antibiotics and resuscitation for septic and suspected septic patients in their care.

An evolving understanding

Any improvements have to be viewed in light of limited progress and continuing mortality. What has been accomplished in sepsis research in the last 40 years? Goal-directed resuscitation and antibiotics reduce morbidity and mortality. Indirect evidence suggests that exposure to a septic source over time increases the collateral physiologic damage and overall organ dysfunction burden. However, the "goals" of resuscitation and timing of antibiotic therapy remain controversial. Adequate resuscitation underlies early sepsis care, but clinicians have crude and uncertain tools to guarantee that resuscitation is adequate. A fixed goal such as a mixed venous saturation greater than 60% may not be as important as attention to other clinical signs in an unstable patient. Recent, well-designed randomized-controlled trials (17, 18, 19) suggest that goal-directed resuscitation algorithms may not be as critical to sepsis care as previously thought. Aggressive early antibiotic administration can lead to improper use of antibiotics when a diagnosis of sepsis is unclear, as might occur with an exacerbation of congestive heart failure that is confused with pneumonia.

Previous investigations document multiple failed therapies. Many of these studies involved inflammatory mediators following the theory that the inflammatory response to infection leads to organ dysfunction in sepsis. A long list of failed therapies, including anti-TNF alpha, ibuprofen, anti-IL-2, branch-chain amino acids and, most famously, drotrecogin alfa (activated protein C), suggests that not only is a single magic bullet for sepsis unlikely, but that the model for therapeutic intervention may be wrong. Although inflammation is a key component of sepsis syndromes, immune suppression, altered endocrine activity and decreased autonomic signaling appear to influence disease progression. Since the septic patient who dies does so in a state of chronic critical illness with multiorgan failure, a new model of disease and therapy is necessary. Sepsis patients manifest neuroendocrine exhaustion, immune dysfunction and energy failure. These findings may provide an opportunity for intervention. In the future, therapies targeting the central nervous system, hormones, or inflammatory cell apoptosis may improve outcomes more than therapies targeting inflammation.

An administrative issue

Given the substantial impact that sepsis has on morbidity and mortality, efforts should continue in the fields of aggressive management and research. The successes of the *Surviving Sepsis Campaign* argue that recommendation bundles directed at evidence-based and standardized care make a substantial difference. There is, however, a caveat. The failures in sepsis management, documented by the long list of failed anti-inflammatory therapies, suggest that simple, single solutions will not be enough to change the course of disease for many patients. Controversy continues around resuscitation and antibiotic therapy. Many adjunctive therapies, such as glucocorticoids, tight glycemic control and pulmonary artery catheter-directed resuscitation have not fulfilled the promise they had 10 years ago. Are we too easily tempted to throw ineffective therapies at a largely insoluble problem? Clinicians may be willing to embrace an uncertain therapy just to be able to do something. They want to be optimistic.

At an administrative level, problems like sepsis are an opportunity for regulation, standardization and general control. Pundits argue eloquently that care variability is the problem and that standardization lets more patients get better care. Guidelines that are useful tools to help clinicians manage complex problems also restrict their ability to respond uniquely to special circumstances. The more recent studies of protocol-driven sepsis care cast doubt on the effectiveness of this approach (17, 18, 19). In the case of sepsis, standardized care can improve outcomes, but should not be taken for granted. The failures in sepsis tell a story about a quest for an easy solution that sometimes misses the important elements altogether. Re-thinking the problem might reveal elusive opportunities.

Conclusions

Sepsis is a syndrome with multiple etiologies and manifestations. Although commonly described in terms of its inflammatory characteristics, effects of sepsis are broad reaching, involving immune, neurologic, endocrine and metabolic changes. Moreover, sepsis is a critical moment in a patient's overall hospital trajectory. Unchecked sepsis, inadequate source control and severe secondary injuries put a patient at risk for transition to a chronic critical illness state and a worsening of morbidity and mortality. As anesthesia providers, we must be prepared to deliver the best care to patients with sepsis, participate in the discussions about its causes and treatments, investigate new ideas, and generate and promote measures that can improve outcomes. Our unique skills in critical care and resuscitation make us ideally suited to these tasks. We understand as well as any physician the complex nature of medical therapies, the assets and liabilities of guidelines, and the need to think critically about them during care and consultation. We can continue to care for septic patients with fluids, vasopressors, inotropes, cultures, advanced monitoring and antibiotic therapy while supporting organ function. As clinical experts in neurosciences, anesthesiologists have an opportunity to investigate new means of treating sepsis. Finally, as experts in safety and guidelines management, anesthesiologists should offer valuable expertise to future guidelines efforts.

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ANESTHESIOLOGY 2017
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Creating Aligned Incentives in Healthcare: What Does and Doesn't Work?

David A. Lubarsky, MD, MBA **Miami, Florida, USA**

Health care expenditures amount to almost $3 trillion (18% of GDP) in the U.S. economy. It is a fragmented industry, however, with hundreds of thousands of employed or independent wage earners (i.e., providers) operating inside of health care systems dedicated to maximizing profit and/or pursuing a social mission. More than 50% of health care expenditures are concentrated in hospital and physician services. Despite this majority share, incentive systems are often poorly designed within health care delivery, primarily because key concepts and principals are loosely understood and applied.

It is well known that a combination of both intrinsic and extrinsic motivators are far better than extrinsic motivators alone, regardless of whether the goal is to be more productive (e.g., see more patients) or more effective (e.g., deliver quality care more consistently). Extrinsic motivators include: raises, promotions, bonuses, demotions, publicized or personal employee recognition, job renewal, etc. Intrinsic motivators, shown to be more important to workers in a cognitive field such as medicine (quote surprising facts about what motivates us on UTube), are often absent. A shared common purpose for the common good is hard to beat when it comes to motivation. While communicating on this matter is essential, words alone are insufficient and demonstrating a true commitment to the enunciated goals must be present routinely, and that is where health system administrations often fail. Even when health systems use extrinsic motivation, they fail to maximize the potential impact because of incorrectly applying well established concepts within financial incentives. Very few incentive systems in health care utilize these proven features gleaned from studying incentives and behavioral economics in non-healthcare settings: finding outcomes that matter by engaging those being incentivized, setting incentives at a sufficiently high level to engage participants (at least 15% of total income, "enough to notice" threshold), avoiding jousting (competitive, i.e. "top 3") incentives that diminish teamwork, not devaluing current work with demeaning incentives ($2/extra RVU, paradoxical reduction in productivity), limiting the number of outcomes being measured that require the attention of caregivers, paying incentives in a timely fashion to avoid hyperbolic discounting, valuing penalties 2x higher than positive incentives (fear of loss), addressing the endowment effect (always valuing more that which you already have), and accounting for the self-extinguishing nature of incentives (the first dollar of incentive is more powerful than the second as the first dollar builds your wealth so the second dollar comapratively is not as valuable).

Well structured incentives that reward performance at the intersection of organizational priorities and physician motivations are well positioned to spur behavioral change and accomplish organizational goals [1]. Combining well structured communication and commitment with extrinsic financial motivators is best. One should not assign dollars to a pro-social or inherently interesting task, as that moves adherence to a goal from a social requirement and non-market assessment to an economic decision. An example of this is the controlled Haifa experiment in 10- pre schools where tardy pick-up was a problem. When parents were fined a small amount for showing up late, tardiness exploded because the parents accepted the late baby-sitting fee so they could run more errands. The social responsibility of being a good citizen and concerning themselves with the impact of their tardiness on the teacher was replaced with a market transaction. One could probably imagine seeing this occurring with fining physicians a small fee for being tardy to clinic. On the other hand, non-negotiable standards and absolute consequences are ok – e.g. loss of a job for forgetting three times to deliver pre-incisional antibiotics after appropriate warnings. That is different than rewarding standard of care with an incentive, or even fining caregivers as above. It is still an extrinsic motivator, but one so large (loss of a job) that it demands adherence.

Financial incentives induce physicians to perform better in terms of productivity and efficiency; the other parts around teamwork, quality of care, and timeliness need to be moved from market based to a non-market based approach. That is how the University of Utah was able to drive physician satsifaction scores to the best in the nation simply by publishing all patient comments openly. Everyone agreed high patient satisfaction with the physician was a common goal – increasing organizational success while providing a high level of patient centric empathic care. The intrinsic motivation of each and every physician to be the healer and excellent doctor they are in their own mind was enough to change behaviors in a way no financial incentive could.

It is important that employers should continuously look for ways to ensure that incentive plans are fair, reward the right behaviors, and are created in a manner that will not dampen teamwork or the commitment to practice excellent medicine. The employee should have control over whether they achieve the goal and reward goals that can be objectively measured. These dynamics and some other features below must be considered to develop the right conditions under which physicians will respond to incentive programs.

The Folly of Rewarding A and Hoping for B

Incentives should reward what you really want. For example, if you want a higher hospital contribution margin, but reward surgeons for the number of surgical cases in the OR, you may end up with many underinsured patients getting procedures with implants because those cases lose money and there is often a waiting list for those procedures. More cases, less money. Rewarding individual RVU productivity in anesthesia when you want higher levels of service and teamwork around the hospital. No one ever willingly goes off the floor to deliver complex care at the bedside. Every system delivers exactly what it is designed to do.

Choosing Incentives

It is imperative to find out what the doctors (and other providers involved!) value in order to devise meaningful incentives. Choose incentives that do not contradict self worth (being a good doctor), help with adminstrative evaluation (things measured on hospital and physician compare, or Leapfrog or that drive federal programmatic incentive systems), or programmatic focus (departments workign together to devise scheduling paradigms to collaboratively work together to drive up appropriate "clinic visit to surgery" conversion rates).

Understanding Ideal Financial Incentive Construction

Metrics asociated with finanical incentives should be aligned to those that are clinically meaningful and easily understood [2]. Accordingly, they should incorporate the following areas: productivity and resource utilization. The following are best treated by other means:

rule-following, patient satisfaction, teamwork and the halting of disruptive behaviors. Kamenica (2012) opines that paying for inherently interesting tasks, paying for prosocial behavior, paying too much, paying too little and providing too many options can all be counterproductive. [3] Proper design of the decision-making environment is a potent way to encourage best behaviors. [4] This conclusion is upheld by a recent study that supports public recognition and real-time data feedback (in combination with financial incentives) as a positive reinforcement to drive physician behavioral change[LDA1]. [5]

Worker Behaviors and Limitations

Generally, three to five goals are preferrable and, they should be specific with measurable endpoints. Difficult (stretch yet achievable goals) generate higher performance than easy or impossible goals. To that end, there are specific rules for goal-based incentive plans, briefly summarized below:

- Worker participation in setting the goal and belief in the worthiness of the goal elicits increased commitment, motivation and common purpose
- On-going, periodic feedback will increase levels of performance
- The worker must believe that the reward will be delivered without any other condition
- The desired change management process should be a social experience as opposed to a top-down initiative

Notably, programs are structured to reward all levels of performance between baseline and goal, in recognition that individuals work harder when they are closer to achieving a goal but reduce their effort when it is farther away or viewed as unachievable [6]. If the amount of incentive being earned is "in the bank" in some ledger shared with the providers, individuals will work even harder not to let that amount slip (so won't pile on vacation if it means diminishing their "earned" incentive). Mental accounting, the endowment effect, fear of loss all are potent behavioral economic principles invoked here.

Understanding Where Financial Incentives Work in a Change Management Process

Financial incentives to physicians are increasingly used to reward peak performance and are a motivational "carrot". To gain a deeper understanding of where they work, familiarity with Kotter's eight steps of change and Max Weber's Four Models for Social Action is warranted. Each theoretical construct a way to think about the conditions under which physicians respond to incentive changes.

Kotter's Eight Steps Process for Leading Change

- Increase urgency
- Build the guiding team
- Get the right vision
- Communicate for buy-in
- Empower action
- Create short-term wins
- Consolidate improvement/sustain acceleration
- Institute change

Max Weber's Four Models for Social Action

- Tradition
- Self-Interest
- Affection
- Shared Purpose

For example, in Kotter's change management paradigm, getting complex systems to change cannot be managed with a simple incentive. Incentives can promote "increased urgency" to the problem, and "consolidae improvement/sustain acceleration" but alone would do little.

In general, financial incentives are one way to communicate organizational priorities to physicians. There are several examples where financial incentive have worked in this regard - supporting population health incentives controlling cost growth and improving performance on a select quality measure, e.g. smoking cessation, hospital readmission and/or preventive care. [7, 8, 9, 10] All of them were informally connected to a complete change management strategy and generated sufficient $ to exceed the "ehough to notice" threshold for those governing the care delivered. In each meta- analysis, we observed that changes were consistently greater for target vs non-target conditions [for patients] at the incentivized hospitals but not at the other hospitals. [11] High quality is an inherent good that might be treated as effectively with motivation and clear publication of performance as well, but that was not studied. It is clear that ranking systems (Safety in Leapfrog, Hospital Compare) do drive behavioral and organizational change even without financial implications.

Physicians, as professionals, resist challenges to their autonomy[12]. Yet, research categorically supports that benchmarking (the use of external data to measure an internal process) is a very powerful tool as it impacts a physician's self-worth. Scholarly studies also conclude that the "social norms" of excelling seem to drive physicians the most as we are receptive to the use of comparative data (i.e. Press Ganey Scores). There is also a plethora of empirical evidence that illustrates how nonstandard interventions might work.

It is important to observe that no single strategy or programmatic focus shows any clear advantage as compared to another; however, comprehensive interventions that combine cognitive, behavioral, and affective components are more effective than single-focus interventions. [13]

Conclusion

This presentation will directly address the questions of which incentive systems in health care have been studied, which have succeeded or failed, and what are the major predictors of success or failure. This comprehensive review is grounded in the framework of ideal incentive construction and behavioral economics principles.

In sum, the crafting of a successful incentive plan (which can effectively influence a physician's clinical decisions) incorporates the use of monetary gain but, more importantly, includes education, behavioral feedback, social pressure, and intrinsic motivators. [14]

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ANESTHESIOLOGY 2017
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Emergency Manual Implementations and Uses During OR Crises

Sara N. Goldhaber-Fiebert, MD **Stanford, CA**

Defining the Problem

During critical events in the operating room (OR), clinician actions can significantly impact patient outcomes.[1] For many life-threatening events, such as cardiac arrest, malignant hyperthermia (MH), or local anesthetic systemic toxicity, there are stacks of published literature on optimal management details. Yet, for rare crises, even expert clinicians often omit or delay key actions, with detrimental impacts on patient morbidity and mortality.[2] In multiple simulation-based studies, correct performance of key actions dramatically increased when emergency manuals (EMs), crisis checklists, or cognitive aids were used.[3-5]

While the dissemination, adoption, implementation, and clinical use of EMs are relatively recent, their use is spreading rapidly in many settings worldwide. The Emergency Manuals Implementation Collaborative (EMIC) provides a central location for implementation and training resources as well as links to cost-free downloadable tools and published literature on rationale from multiple industries.[6] This ASA Refresher Course (RCL) integrates the known evidence on EMs from simulation-based OR studies and from pertinent use in other safety-critical industries like aviation, a conceptual framework for clinical implementation, and emerging data from perioperative clinical implementations and uses.

Emergency Manuals as Enabling Tools

Emergency manuals, which are context-relevant sets of cognitive aids such as crisis checklists, provide professionals with key helpful information for managing rare critical events (see EMIC at www.emergencymanuals.org). EMs are intended as both educational and clinical tools. For simplicity, the term *emergency manual* (or EM) will be used throughout this RCL, though the overlapping terms *crisis checklists*, *emergency checklists*, or *cognitive aids* are often also used interchangeably in referring to such tools. EMs are intended to be symbiotic adjuncts with, rather than replacements for, good preparation, teamwork, and judgment. EM use should never precede necessary immediate actions such as chest compressions for a pulseless patient. Their intended use begins once resources allow—either sufficient help is available for synchronous use at the beginning of a crisis, or initial clinical actions are already underway. Figure 1 shows EMs being used during simulated critical events.

Figure 1. Emergency Manual use by anesthesiologists during simulated critical events. Photos ©D. Gaba left, S Goldhaber-Fiebert right, reprinted with permission

Learning from Other Industries

Safety-critical industries, such as aviation and nuclear power, routinely integrate emergency manuals into their training exercises, and professional teams are expected to have available and use EMs during real critical events, after "immediate actions" are begun. The human factors and psychology literature repeatedly demonstrates that memory retrieval is impaired for rarely used information, particularly under stressful and time-sensitive conditions, which makes relying on memory alone a risky strategy. Even when expert professionals know the correct management decisions under standardized testing conditions, these same experts are often not able to deploy this detailed management knowledge under stress.[7,8] Common errors during management of simulated OR critical events

include both diagnostic and therapeutic cognitive errors,[9] and also cognitively recalling but never completing the action. One of the reasons for the latter is prospective memory error—forgetting to do something you intended to do—common because prospective memory is vulnerable to interruptions, which are frequent during crises.[10] In early clinical experience, the use of EMs—combined with good training, teamwork, and judgment—is helping to bridge this gap, via multiple mechanisms, to help teams deliver optimal care during critical events.[11-13] However, rigorous larger studies using mixed quantitative and qualitative methods are needed to further understand clinical implementation and use of EMs.

Four-Element Framework

Our prior work provided a conceptual framework for clinical implementation of emergency manuals by analyzing their implementation and use in safety-critical industries along with early data from healthcare.[14] The framework is relevant for EMs, and similar patient safety tools, because having a tool to implement is a necessary start, but is vastly insufficient for enabling effective use.

The four elements for implementation of EMs, which overlap and interact nonlinearly, are (Figure 2):

1. *Create* (or locally customize an available manual): Provides the EM content and design of what to implement (*i.e.*, a tool)
2. *Familiarize*: Train clinicians including why, as well as how and when to use
3. *Use* clinically: Includes accessibility in all needed locations as well as team–EM interactions, *e.g.*, triggering EM use and "reader" role
4. *Integrate*: Local safety climate or culture strongly influences clinician behavior, as described in the field of implementation science[15]

As with other improvement efforts in healthcare, early experiences show that addressing these vital elements is greatly enabled by leadership engagement, local champions, and inter-professional implementation teams.[16,17]

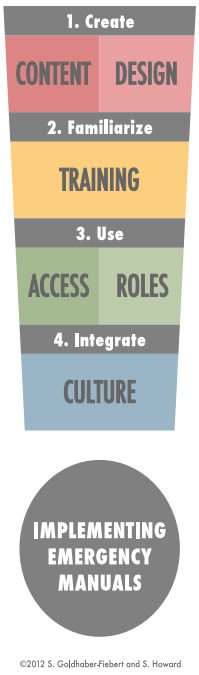


Figure 2. Four vital elements for implementing emergency manuals. ©S. Goldhaber-Fiebert & S. Howard, 2012, reprinted with permission

Figure 3. Crisis Resource Management (CRM) teamwork and dynamic decision-making interacting skills, including "Use cognitive aids." Reprinted with permission

Why Now?

History

Emergency manual use builds synergistically upon prior patient safety and quality improvement developments in healthcare over the past few decades, and even century. The concept is not itself new, the first known mention being nine decades ago. In 1924, *Anesthesia & Analgesia* published a manuscript by Dr. Wayne Babcock (famous surgeon of the Babcock forceps) entitled "Resuscitation during Anesthesia."[18] In it he states, and I categorize here by concepts discussed above:

> *"If a response is not instantly obtained by simple measures* (= immediate actions), *a fixed emergency routine* (= an EM or similar tool based upon best known data) *posted on the walls of every operating room* (= accessible where needed) *and drilled into every member of the staff should be enforced"* (= prior training along with a culture of expected use, albeit he emphasizes here top-down enforcement over other important cultural influences).

While a full history of simulation, teamwork training, cognitive aids, and checklists is beyond the scope of this module, some further background on each is provided in the Reference section (see references 10 and 19–23). In his 2014 *ASA/APSF Ellison C. Pierce, Jr., MD, Patient Safety Memorial Lecture* entitled "Competence and teamwork are not enough: the value of cognitive aids," Dr. David Gaba provides a detailed description of how EMs developed in anesthesiology and healthcare from a rich, broader history of cognitive aids and checklists.[24] Figure 3, on Crisis Resource Management, shows visually how all use of cognitive aids exists within the broader context of teamwork and dynamic decision-making skills.

Availability

For many years, Advanced Cardiac Life Support cards and Malignant Hyperthermia posters were the only readily available cognitive aids for OR critical events. In the past few years, development work by multiple groups in parallel has provided cost-free access to several emergency manuals or crisis checklists designed for use in the OR during crises.[25] See Figures 4, 5, and 6 for examples of these tools.

Dissemination and Clinician Receptivity

Dr. Atul Gawande's popular book *The Checklist Manifesto*,[22] along with multiple healthcare implementations and studies regarding routine use of checklists, all influenced the receptivity of clinicians and healthcare institutions to the concept and potential benefit of emergency manuals.[26,27] When Dr. Babcock initially proposed the concept, at least for cardiac arrest, more than ninety years ago, the healthcare community was not yet ready. In contrast, the message of potential EM utility is now spreading quickly. The November 2013 issue of *Anesthesia & Analgesia* focused on the topic with three articles and two editorials on EMs, cognitive aids, or crisis checklists. Numerous articles in the American Society of Anesthesiologists (ASA) and Anesthesia Patient Safety Foundation (APSF) newsletters, as well as conference presentations, spread the word efficiently and, along with multiple research studies, piqued interest in a healthcare community now ready to effectively use these tools clinically. In September 2015, APSF held an experts' conference focusing on EM evidence, implementation, and use.[17] Since the Emergency Manuals Implementation Collaborative was founded in 2012, the combined downloads of EM resources from Stanford University, Harvard's Ariadne Labs, and the Society for Pediatric Anesthesia totaled more than seventy thousand in English, and hundreds of thousands including translated versions. (EMIC Steering Committee, personal communication, October 24, 2016). Many users stated they then shared the content with numerous colleagues at their local institutions, implying much broader dissemination. Clebone *et al*. recently described the development, simulation testing, and broad dissemination of the Society for Pediatric Anesthesia Critical Events Checklists.[28]

Summary of Simulation-Based Data

There is now a decade of studies examining whether the use of emergency manuals during realistic mannequin-based simulation scenarios helps clinicians perform better during these crises. The preponderance of the data points to yes, although there are clearly important nuances involved in *how* to best use these tools. Some of the most relevant studies are described here.

In a 2006 observational study of anesthesia residents managing simulated MH cases, Harrison *et al.* found a positive correlation between the frequency of MH cognitive aid use and appropriate treatment of MH.[3] Burden *et al.* found that a majority of anesthesia and obstetrics residents did not use easily accessible cognitive aids, and

proceeded to omit key actions during management of MH and obstetric cardiac arrest simulated scenarios. When a medical student "reader" was explicitly charged with reading to the team from the cognitive aid, key actions were then performed and the help appreciated—raising the question of how teams can trigger appropriate use and reader roles themselves.[29] Bould *et al.* found no difference in the management of neonatal resuscitation with or without a cognitive aid poster, but importantly, subjects were not familiar with the poster before the scenario and most in the "intention to treat" intervention group did not use it frequently, *i.e.*, if it is not used, it cannot help.[30] Neal *et al.* found that anesthesia residents performed significantly better in managing a surprise scenario of local anesthetic systemic toxicity (LAST) when randomized to have access to a previously introduced, and therefore familiar, LAST checklist *versus* not having access to the checklist. Moreover, within the intervention group, the residents who used the LAST checklist more frequently performed even better.[4]

Arriaga *et al.* studied interprofessional OR teams managing eight different OR crises. Each team was randomly assigned to half of the events with, and half without, crisis checklists, serving as their own controls. The teams were familiarized with the crisis checklist concept and format, though not the specific events. When crisis checklists were available, 6% of key management steps were missed *versus* 23% when they were not, signifying a large improvement in event management.[5] Marshall broadly reviewed the cognitive aid literature and also discussed the impact of design factors for cognitive aids in healthcare.[31] Following this review, Marshall's group conducted multiple simulation studies to delve into the impacts of cognitive aid designs and use on team functioning and nontechnical teamwork skills.[32,33] Watkins *et al.* studied paper versus electronic versions in simulated settings at an institution without clinical implementation, but with a brief familiarization just prior to use. They found about a third did not use the tool at all, and that neither version had a major impact on performance, though pointing out that effective use of cognitive aids is greatly impacted by training and implementation as well as design of the specific tool.[34,35] Goldhaber-Fiebert and Howard put the healthcare literature into context with findings from other safety-critical industries and decades of iterative simulation-based development and testing, proposing the four-element implementation framework described above.[14]

Early Clinical Implementations: Data and Resources

Neily *et al.* surveyed Veterans Health Administration (VHA) anesthesia professionals six months after national VHA implementation of a 14-event clinical cognitive aid for OR critical events, which was initiated at the VA Palo Alto Health Care System, drew on prior work from the book *Crisis Management in Anesthesia*, and was a precursor of the Stanford Emergency Manual.[10,36,37] Of the respondents, six months after clinical launch 87% knew the tool existed, half had used it as a reference, and 7% had used it during a crisis. Among crisis users, all had used the aid previously as a reference, which likely improved familiarity with and awareness of the tool, and all felt it was helpful. Training varied across VHA sites, and crisis users were more likely to have received prior formal training.[36] While 7% may not sound like much, the relevant denominator of applicable critical events in the six months since implementation is not known and likely is itself small, with only a subset of respondents even encountering an applicable opportunity.

Following recent widespread cost-free dissemination of the Ariadne Labs' crisis checklists,[38] Stanford Emergency Manual for Perioperative Critical Events,[37] and the Society for Pediatric Anesthesia's critical events checklists,[39] there have been case reports[12,13] as well as many personal emails and stories told about effective clinical uses of EMs during clinical critical events. The common emerging themes include:

- Importance of EM accessibility and familiarity
- The need for someone on the team to suggest or trigger use
- Helpfulness of a reader role, separate from event leader, when resources allow
- The potential for EMs to improve team communication

Many potential biases exist when single case uses are described individually. However, the multiple early reports do suggest that these tools are being used clinically and that at least some clinicians have found them to be helpful for patient care, underscoring the need for more formal mixed-methods research on clinical implementation and use of EMs.

Research on clinical implementation for EMs is nascent, with our team recently reporting a study of early clinical uses with mixed-methods survey data from Stanford anesthesia residents before and 15 months after clinical launch.[11] Residents reported that OR safety culture supporting appropriate use of cognitive aids improved since clinical launch, and that the most impactful training exposures were mannequin-based simulations of critical events coupled with self-review. Of surveyed residents, 19 (45%) had used an EM during a clinical critical event, which—if conservatively presuming zero use by non-responders—still translates to at least a quarter of all residents. The

vast majority of users felt the EM helped their teams deliver better care to their patient, and none felt it hurt or distracted from care. A figure in that article shows the wide variety of events for which EMs were used.

When our team assessed the impact on OR staff trainings for EMs and teamwork skills of *in situ*, low-tech simulation, we found increased awareness of, familiarity with, and intention to use EMs in the future.[40] The full curriculum, instructor's guide, and handouts are available through MedEdPORTAL.[41] Multiple groups have published or shared other online video-based training materials for why, how, and when to use EMs effectively.[42-43]

As more institutions pursue EM implementation locally, discussions reveal that common important factors include: leadership engagement, local champions, inter-professional implementation teams, training including rationale along with use details, and local customization, at least for key telephone numbers and conformity with local policies.[17]

Conclusion and Next Steps

Perioperative medicine has reached a tipping point for enabling effective use of emergency manuals to help teams deliver better patient care during critical events. The evidence base from other safety-critical industries and from simulation-based studies has shown that there is a need, and that EMs can fill this need when used effectively during crises. Multiple cost-free tools are now widely available for clinical settings, along with implementation and training resources. As research on clinical implementation expands, among the next priorities are to:

- Understand dissemination, adoption, and implementation
- Study the impacts of clinical uses
- Assess barriers and facilitators for EM implementation and use
- Share effective implementation, training, and use strategies
- Actively seek out and mitigate any potential harms

These goals will require rigorous mixed qualitative and quantitative methods from implementation science combined with well-planned local quality improvement efforts. The data described here suggest a promising role for EMs in helping teams deliver optimal care to patients during critical events, which is worthy of further exploration.

Examples of Free Tools (all linked from EMIC website www.emergencymanuals.org)

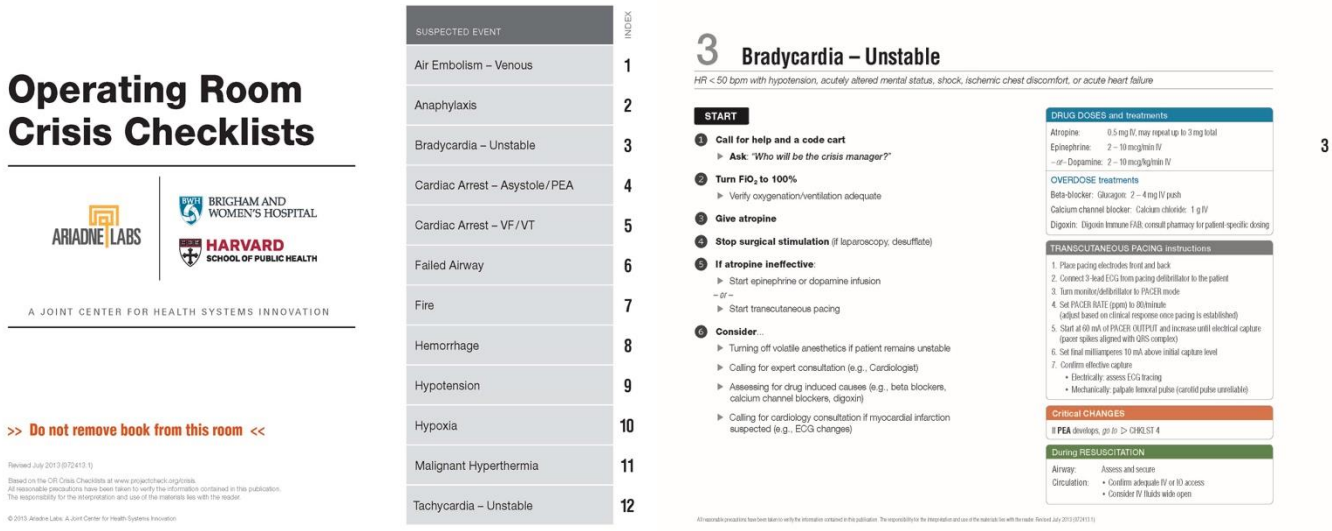


Figure 4. Table of contents and sample page from the Operating Room Crisis Checklists, from Ariadne Labs. For latest version see: http://www.projectcheck.org/crisis.html.

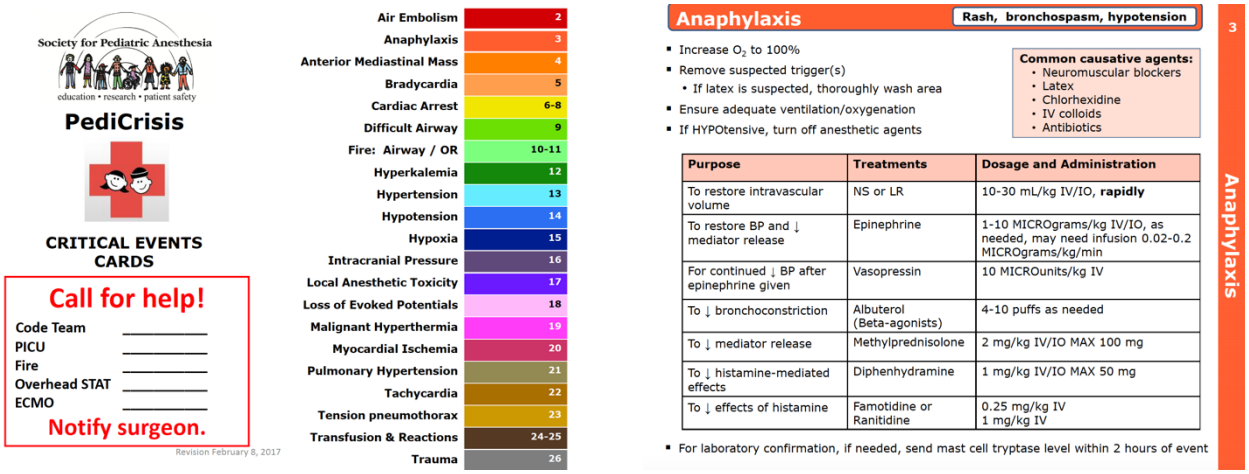


Figure 5. Table of contents and sample page from the PediCrisis Critical Events Checklist, from the Society for Pediatric Anesthesia's (SPA) Quality and Safety Committee. For latest version see: pedsanesthesia.org, Quality and Safety Committee, Critical Events Checklists.

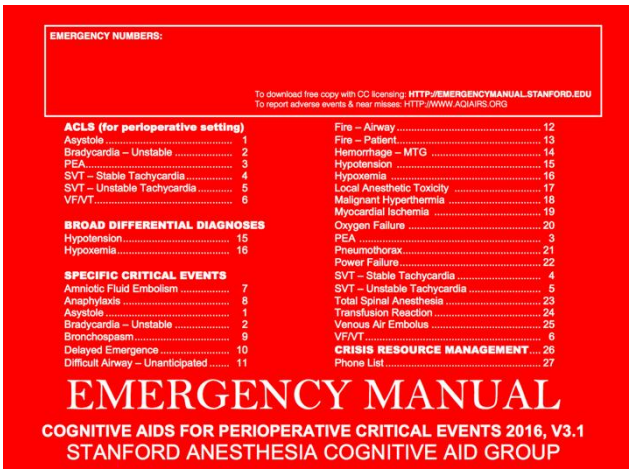
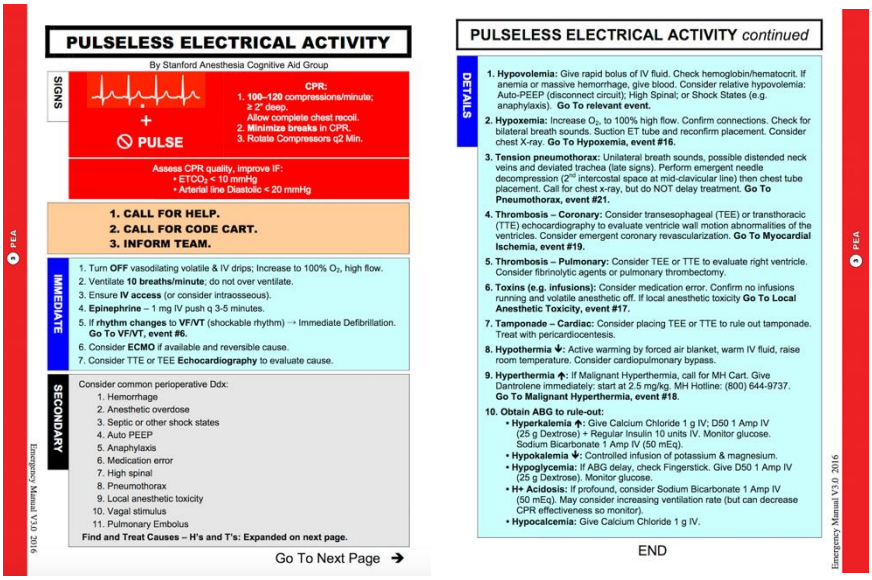


Figure 6. Table of contents and sample page from the Stanford Emergency Manual for Perioperative Critical Events by Stanford Anesthesia Cognitive Aid Group (SACAG).

For latest version see: http://emergencymanual.stanford.edu.



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Obstructive sleep apnea and anesthetic pharmacology-clinical concepts

Evan Kharasch, MD PhD **St. Louis, MO**

Background

Obstructive sleep apnea (OSA) is characterized by repeated partial or total airway obstruction in the presence of ventilatory efforts, accompanied by oxygen desaturation. OSA affects a substantial portion of adult and pediatric surgical patients, with important implications for intraoperative and postoperative care. OSA, characterized by intermittent collapse of the upper airway, is one type of sleep disordered breathing; the other type is central sleep apnea, with episodic loss of ventilatory drive. OSA patients have coexisting cardiovascular, cerebrovascular, and metabolic disease. OSA patients have a greater incidence of postoperative cardiac and pulmonary complications and increased intensive care unit admissions.[1,2]

This monograph will focus specifically on the pharmacology of benzodiazepines, sedative-hypnotics, opioids, and other analgesics in OSA patients; and the interplay between sleep, pain, analgesia and OSA. While an abundance of reviews, monographs, and guidelines have been written about OSA and anesthetic pharmacology, the number of seminal primary clinical studies is comparatively few. Data from animal studies will not be presented.

Clinical Problem

Clinical apnea is defined as cessation of airflow for at least 10 sec, and is considered OSA if there is ventilatory effort. There is no singular definition of hypopnea, however one common definition is a 30% or more reduction in airflow, for at 10 sec, with 4% or more decrease in oxygen saturation.[3,4] The "Gold Standard" for evaluation of OSA is overnight sleep lab polysomnography (PSG), although there is increasing use of home sleep testing.[5,6] From PSG are obtained the apnea-hypopnea index (AHI), which is the number of episodes of apnea or hypopnea per hour of sleep, and the respiratory disturbance index (RDI), which is the number of episodes of apnea or hypopnea per hour of recording. The magnitude of OSA is classified as mild (AHI 5-15), moderate (AHI 16-30) or severe (AHI>30). In general, the sensitivity of 1 night of PSG to detect AHI≥5 in OSA is 75-88%. Several screening and clinical prediction algorithms have been proposed to predict OSA (e.g. Berlin questionnaire, Epworth sleepiness scale, STOP-BANG questionnaire, ASA checklist). These have 70-90% sensitivity but lower (30-60%) specificity, and the overall quality of evidence for effectiveness compared with AHI is low-moderate.[5,6]

The prevalence of OSA in adults is increasing.[7] The incidence of mild OSA (AHI≥5) is 43% and 28% in males and females 50-70 yr, and 27% and 9% in those 30-49 yr, respectively. The incidence of moderate OSA (AHI≥15) is 17% and 9% in males and females 50-70 yr, and 10% and 3% in those 30-49 yr, respectively. Most (80-90%) patients with moderate-severe OSA are undiagnosed. OSA is more common in obesity. The majority of (60-80%) but by no means all OSA patients are obese, and >70% of bariatric surgery patients have OSA.

The most common site of airway obstruction in adult OSA is the upper pharynx (90%), most commonly the soft palate, and tongue base.[4,8,9] However there may be multiple sites of obstruction, and this occurs with increasing OSA severity and body mass index. Obstruction in the upper tongue base, pharynx, and larynx is mainly anteroposterior, while in the oropharynx it is lateral. With more severe OSA and obesity, obstruction is more circumferential. Obstruction is also influenced by CNS control of upper airway dilator muscles. The genioglossus muscle (tongue) is a critical determinant in maintaining pharyngeal airway patency, particularly in OSA. Compared with non-OSA patients, OSA patients have: 1) structurally narrower and more collapsible pharyngeal airways (and neck fat deposits in obesity cause even more constriction), 2) greater basal genioglossus muscle tone to compensate for narrower and more collapsible airways, 3) a greater decrease in their genioglossus activity during sleep (non-REM and even more so during REM sleep). REM sleep significantly decreases hypoglossal nucleus and genioglossus muscle activity, and pharyngeal muscle tone, predisposing to airway obstruction. Thus OSA can occur in non-REM sleep and REM sleep, and can be more extensive in the latter.

OSA in children is different than in adults.[10,11] The population incidence is 1-6%, but is as high as 36% in obese children. Pediatric OSA has different pathophysiology and treatment compared with adults. The principle etiology of pediatric OSA is upper airway obstruction by enlarged tonsils and adenoids. These are largest in relation to the

upper airway size between 3-6 yr, corresponding to the peak incidence of pediatric OSA. Craniofacial abnormalities may also be an additive risk factor. Abnormalities in CNS control of upper airway dilator muscles also appear contributory, as in adults. Normal children can maintain inspiratory airflow at even sub-atmospheric pressures (Pcrit, the pressure at which airway collapse occurs), but those with OSA have a Pcrit in the positive range (and this does not normalize after adenotonsillectomy). Thus pediatric OSA patients may have impaired ability to maintain adequate neuromodulator airway tone. Adenotonsillectomy is the primary therapy for pediatric OSA. A recent meta-analysis found that lingual tonsillectomy had a mean reduction in AHI of 9 events/hr, a 6% increase in minimum oxygen saturation, and an overall success rate of 51% for a postoperative AHI<5 and 17% for AHI<1. Nonetheless, there is often residual OSA.[12]

OSA patients have episodic pharyngeal airway obstruction during sleep, with consequent nocturnal intermittent hypoxemia, hypercarbia, sleep fragmentation, and sleep arousals. The critical pathophysiologic determinants of upper airway patency are anatomy and pharyngeal muscle tone (which is more variable, both tonic at rest and phasic during respiration).[13,14] The genioglossus muscle is the most critical determinant in maintaining pharyngeal airway patency, particularly in OSA.

Normal deep non-REM and REM sleep reduces central drive, decreases upper airway muscle tone, and at critical airway pressure the pharynx collapses. Postoperatively, sleep architecture is disturbed. REM sleep is decreased immediately post-op, and "REM rebound" occurs days later.[3,15-17] This occurs both in non-OSA and OSA patients. In both OSA and non-OSA patients, postop sleep architecture (sleep efficiency, REM sleep, slow-wave sleep) was decreased on night 1, and sleep-disordered breathing (AHI) was worse (maximal on night 3).[17]

The critical reliance on neural input to the genioglossus and its decrease during sleep, together cause airway obstruction during sleep in OSA. Hence, there is a considerable amount of interest in, and concern regarding, the effect of anesthetic and analgesic drugs on neural input to the genioglossus, and the potential effect of REM rebound, and potential airway obstruction.[3,15,16]

Pharmacology

The influence of OSA on the pharmacology of sedative hypnotics, benzodiazepines, and opioids has been the subject of innumerable reviews. For a sample, see.[18-27] There are comparatively fewer well-controlled clinical investigations.

Sedative hypnotics (ethanol, benzodiazepines) and general anesthetics (propofol and volatile, even in sub-anesthetic concentrations) are considered to cause dose-dependent decreases in central neural input to pharyngeal dilating muscles (genioglossus, geniohyoid), airway muscle tone (disproportionately decreased relative to the diaphragm), airway patency, and the arousal response.[18,19,27]

Propofol, in healthy individuals, causes dose-dependent central inhibition of genioglossus muscle tone, and decreases upper airway cross-sectional area in proportion to the depth of anesthesia.[25,28] Obstruction was greatest at the base of the tongue, and in an anteroposterior direction.[25] In contrast, phasic genioglossus EMG activity was sustained with increasing propofol concentration, but decreased abruptly to minimal values with loss of consciousness.[29] Propofol sedation caused more airway collapse and obstruction in OSA patients compared with non-OSA habitual snorers, with greater frequency of collapse at the base of the tongue, soft palate, or both.[30] However, when evaluating polysomnography in OSA patients, there was no meaningful difference between natural sleep and propofol sedation in the AHI, mean arterial oxygen saturation, or lowest oxygen saturation.[31]

Few studies have rigorously evaluated benzodiazepine effects in OSA, and airway effects in normal individuals are reportedly small.[25] In one comparison of normal weight adult OSA patients and healthy volunteers, undergoing polysomnography during both overnight sleep and midazolam sedation, midazolam overall had no effect on OSA (AHI or lowest oxygen saturation).[32] In contrast, the midazolam dose required for sedation was significantly lower (0.06 ± 0.05 vs 0.09 ± 0.05 mg/kg) in patients with moderate-severe OSA (AHI≥15 events/hr) vs mild or no OSA (AHI<15 events), and OSA was an independent predictor of low midazolam dose, independent of BMI.[32] Similarly, in patients with severe OSA, the median dose to cause loss of consciousness was also low - only 1.0 mg (range 0.6-1.2).[33] However the critical closing pressure (Pcrit) was comparable after midazolam and during overnight sleep.[33] In OSA patients, the reduction in genioglossus muscle EMG from awake to sedation with midazolam was less than the reduction during natural sleep.[34] Together, the available evidence suggests that OSA patients are more sensitive

than non-OSA patients to sedative effects of midazolam. However midazolam in OSA compared with non-OSA patients does not cause greater changes in airway tone, increase pharyngeal collapsibility or worsen OSA severity.

Even fewer studies have evaluated other sedative-hypnotics or anesthetics in patients with OSA. Dexmedetomidine is generally considered to have less effect on upper airway cross-sectional diameter than sedative-hypnotics and benzodiazepines.[25] In 50 normal weight adults with moderate to severe OSA, in a crossover comparison of dexmedetomidine and propofol, partial or total airway obstruction observed in all patients during sedation, but there was no difference in the degree of obstruction with dexmedetomidine vs propofol. Oxygen desaturation however was less frequent and severe with dexmedetomidine vs propofol.[35] Volatile anesthetics are considered to decrease cross-sectional airway diameter and cause upper airway collapse,[36] however little data exist regarding the influence of OSA on these effects.

Opioid effects in patients with OSA have been the subject of considerable attention, speculation, and recommendation. Opioids do routinely increase the apneic threshold, diminish the hypercapneic and hypoxic responses, and decrease ventilatory drive in patients.[26] The seminal question is whether these effects are greater in patients with OSA. Many reviews suggest that opioids increase the risk of airway obstruction in patients with OSA, and recommend against using opioids in OSA patients.[37-41] Nevertheless, few human studies have assessed acute opioid effects on airway tone and breathing, and even fewer in OSA.[42] In healthy (non-OSA) pain-free adults, hydromorphone had no effect on either awake pharyngeal resistance or breathing during sleep (apnea, hypopnea),[43] and morphine had no effect on breathing during sleep.[44] In postoperative patients at risk for OSA (but excluding patients with known OSA), morphine had no influence on the incidence of obstructive apnea, central apnea, hypopnea or desaturation.[45]

There are few studies of opioid effects in adults with OSA. In polysomnography-confirmed moderate OSA patients, administered either remifentanil (0.075 μg/kg/hr) or saline infusion while asleep, remifentanil had no effect on the severity of apneas or hypopneas, and actually decreased the number of obstructive apneas compared with saline.[46] Remifentanil did impair sleep architecture (decreased REM, increased arousals) and increase central apnea. Thus, contrary to conventional expectation, remifentanil did not increase the risk of airway obstruction in these patients with OSA, and OSA actually improved. The improvement was attributed to decreased REM sleep.[46] In another investigation of polysomnography-confirmed moderate OSA, 30 mg oral morphine at bedtime (vs baseline) caused no significant respiratory depression, no change in the AHI, and no change in the amount of time with SaO_2<90%, while the subjects with higher plasma morphine concentrations had an improvement in AHI and sleep time with SaO_2<90%.[47] Among volunteers with or without polysomnography-confirmed mild OSA receiving a remifentanil infusion, the relationship between lower nadir SaO_2 and greater analgesic sensitivity to remifentanil was said to be significant based on heat pain threshold (suggesting that OSA increased sensitivity to remifentanil), but not based on heat pain tolerance, cold pain threshold, or cold pain tolerance (suggesting that OSA did not increase sensitivity to remifentanil).[48] In postoperative bariatric surgery patients with varying degrees of OSA, there was said to be a significant correlation between lower postoperative opioid consumption and a greater percentage of sleep time at SaO_2<90% (suggesting that OSA increased sensitivity to opioids), but not compared with minimal nocturnal SaO_2 or the AHI (suggesting that OSA did not increase sensitivity to opioids).[49]

In general, these studies did not suggest that adult OSA patients are more sensitive to the airway or ventilatory effects of opioids, and there is mixed evidence regarding the effects of OSA on opioid analgesia. More recent review have concluded *"Current evidence does not support a direct relationship between an isolated preoperative diagnosis of OSA and increased risk for opioid-induced ventilatory impairment during postoperative opioid therapy"*.[26] In addition, the very low incidence of opioid-related postoperative ventilatory events in adults contrasts with the high prevalence of OSA in surgical patients.[24] An even greater unknown is whether any purported changes in the response to sedative hypnotics, benzodiazepines, and opioids in adults with OSA reverts, or persists, in those treated with continuous positive airway pressure (CPAP).

In contrast to adults, there is a generalized perspective that children with OSA are more sensitive to the effects of opioids.[23,50] This perspective emanated originally from clinical experiences in a few children with suspected OSA undergoing tonsillectomy with or without adenoidectomy.[51-54] In a retrospective database review of 46 children, there was a positive correlation between cumulative postoperative morphine dose and the lowest preoperative oxygen saturation.[51] Children with a preoperative SaO_2 nadir <85% needed less morphine than those with a nadir ≥85% (0.062 ± 0.040 vs 0.105 ± 0.031 mg/kg). In a follow-up prospective study of 22 children with suspected OSA undergoing tonsillectomy, with a preoperative SaO_2 nadir <85% needed less morphine than those with a nadir ≥85%

(0.06 ± 0.03 n=6 vs 0.12 ± 0.04 n=16 mg/kg).[52] The article concluded that "children with a history of recurrent hypoxemia display a greater sensitivity to opiates than children who have not experienced recurrent hypoxemia".[52] Some other data support this notion. In intubated children with confirmed OSA, compared with controls, there was increased sensitivity to the ventilatory effects of fentanyl, which caused central sleep apnea. [55] A retrospective review of intraoperative and postoperative opioid requirements of children (3-4 yr) who underwent cleft lip or palate surgery in Cusco, Peru (altitude 3400m) and Lima, Peru (150m), found that opioid dosing was 40% less in otherwise healthy children from Cisco, attributed to altitude-induced chronic hypoxia.[56]

However not all studies agree. Children (2-16 yr) with polysomnography-confirmed OSA compared with children with recurrent tonsillitis, all anesthetized for adenotonsillectomy using a standard protocol, had more airway and respiratory complications but similar postoperative opioid requirements.[57] Among pediatric ambulatory surgical patients, 1/3 of whom had symptoms of sleep disordered breathing (SDB, including witnessed OSA, but not confirmed by polysomnography), those with SDB had higher pain scores, a greater incidence (2-fold) of receiving postoperative (PACU) opioid, and higher opioid doses (not lower), compared with non-SDB patients.[58]

Most reviews articulate that children with OSA have an increased sensitivity to opioids, believed related to chronic hypoxemia.

In 2012, the FDA issued a warning after 3 children who underwent tonsillectomy for OSA and received normal doses of codeine died and another experienced life-threatening symptoms. The children were "ultra-rapid metabolizers" of codeine (to morphine). In 2013, FDA added a *Boxed Warning* to the codeine label cautioning against use in children after surgery to remove tonsils or adenoids. FDA also issued more generalized (beyond OSA) Drug Safety Communications in July 2015 (codeine) and September 2015 (tramadol) warning about risks of serious breathing problems in some children (ultra-rapid metabolizers). In 2017 FDA changed the *Boxed Warning* to a *Contraindication*, for codeine and tramadol, alerting that codeine should not be used to treat pain or cough and tramadol should not be used to treat pain in children younger than 12 years, added a new *Contraindication* to tramadol against use in children <18 yr to treat pain after surgery to remove tonsils and/or adenoids, and a new *Warning* to codeine and tramadol recommending against use in adolescents 12-18 yr who are obese or have conditions such as OSA or severe lung disease. All such notifications are at http://www.fda.gov/drugs/drug safety. The above considerations appear mechanistically related more to opioid pharmacokinetics (ultra-rapid metabolism to active metabolites which are more effective opioid agonists than their precursor prodrugs) than to OSA. The question remains, whether and if so how, children with OSA are pharmacodynamically more sensitive to the effects of opioids?

Postoperative Pain, Analgesia and Sleep Apnea

In clinical practice, the interaction between OSA and pharmacology is even more complex than presented above.[17,59-61] There is a substantial interplay between postoperative pain, altered sleep, and opioid pharmacology. Postoperatively, often as a result of pain, total sleep time is generally reduced for 1 or 2 nights, there is fragmented sleep with frequent arousals and awakenings, the amount of slow wave sleep is reduced for up to 4 nights postoperatively, REM sleep is generally absent on the first 2 postoperative nights, and then there is REM ''rebound'' over subsequent nights. Insufficient sleep quantity (single night total sleep deprivation, selective sleep stage deprivation, or several days of sleep restriction or fragmentation) or disordered sleep can cause inflammation, increased pain, and a lower pain detection threshold.[62] And opioids, although sedating, can disturb sleep. OSA may worsen pain (via sleep disruption and/or chronic intermittent hypoxemia). And disordered sleep can worsen OSA. Withholding adequate analgesia, in order to avoid interactions with OSA, may inadvertently increase pain, and worsen disordered breathing.

The American Society of Anesthesiologists Task Force on Perioperative Management of Patients with Obstructive Sleep Apnea issued Practice Guidelines for the Perioperative Management of Patients with Obstructive Sleep Apnea, initially in 2006,[39] and updated in 2014.[63] The Guidelines note that the literature on OSA patients is insufficient to evaluate the effects of various anesthetic techniques and the outcomes of various postoperative analgesic techniques as they specifically apply to patients with OSA.[63] However, recommendations are then stated. The Practice Guidelines state the Recommendation that because OSA patients are especially susceptible to respiratory depressant and airway effects of sedatives, opioids, and inhaled anesthetics, therefore the potential for postop respiratory compromise should be considered in selecting intraoperative mediations.[63] Similar recommendations to avoid sedative premedication and minimize postoperative sedation have also been proffered.[64] Recommendations for postoperative management

include the use of regional anesthesia, to weigh the benefits and risks of using an opioid or opioid–local anesthetic mixture rather than a local anesthetic alone if neuraxial anesthesia is planned, and to avoid or use with extreme caution background infusions if patient-controlled systemic opioids are used, and to use non-steroidal anti-inflammatory drugs. Recommendations regarding opioids are more variable. A 2008 review suggested that "Although there remains a lack of good evidence on opioid effects in OSA patients, the general recommendation is that opioids should be avoided if possible".[41] In contrast the 2006 and 2014 ASA Guidelines do not state that suggestion. Recent research and reviews suggest that these is not good evidence that adult OSA patients are at increased risk for opioid-induced postoperative ventilatory impairment.[26] These considerations are somewhat different for children undergoing adenotonsillectomy, where codeine and tramadol are contraindicted.

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Neurotrauma Update: Perioperative Management of Adult Head and Spinal Cord Injury Patients

Adult Traumatic Brain Injury

Audrée A. Bendo, M.D. **Brooklyn, New York**

Traumatic brain injury (TBI) is one of the most serious, life-threatening conditions in trauma victims.[1] Prompt and appropriate therapy is necessary to obtain a favorable outcome. Perioperative management of head-injured patients focuses on aggressive stabilization of the patient and avoidance of systemic and intracranial insults that cause secondary neuronal injury. Secondary brain injury complicates the course of the majority of head-injured patients, adversely influencing outcome. These secondary insults are potentially preventable and treatable.

I. Epidemiology

An estimated 1.7 million people sustain TBIs every year in the United States.[2] Of these, over 50,000 people die, and another 80,000 people become impaired or disabled for life. TBI is a leading cause of disability in the United States, affecting approximately 5.3 million people.[2] Head injury occurs most frequently in adolescents, young adults, and people older than 75 years of age. In all age groups, males are affected two times more often than females and are more likely to sustain severe head injury. The leading causes of TBIs are falls, motor vehicle crashes, and assaults.[2] From 2001 to 2010, the rates of TBI-related emergency department visits increased by 70%, hospitalization rates only increased by 11% and death rates decreased by 7%.[2]

II. Head Injury Guidelines

In 1995, the Brain Trauma Foundation approved guidelines for the initial resuscitation of the severe head injury patient and treatment of intracranial hypertension recognizing the need to standardize care to improve outcome in head-injured patients.[3] A task force was formed in 1998 to review and update the scientific evidence for the guidelines. Evidence-based guidelines for the management of severe TBI were published in 2000[4] and updated most recently in the U.K. in 2014[5] and in the U.S. in 2016.[6] The guidelines represent a comprehensive review of the literature and provide the best treatment recommendations for the acute care management of the hospitalized severe TBI patient. However, most of these guidelines are based on Class II or III evidence, and therefore, are consensus-based recommendations.

Evidence-based guidelines for prehospital management of TBI[7], pediatric brain injury[8], and surgical management[9] have also been published. The TBI contributing authors have developed a 'Center for Guidelines Management' which is responsible for generating new guidelines as well as updating existing guidelines. Their mission is to improve outcome of TBI through collaboration and the promotion of evidence-based medicine.[6]

Current guidelines recommend that all regions establish organized trauma systems and protocols for resuscitation. Resuscitation protocols from prehospital to critical care management have been developed and instituted based on available information. This lecture will discuss the various guidelines and new research initiatives to address whether or not implementation is improving outcome. The guidelines and controversies in management will be discussed as we take a patient through the resuscitation protocol as described in Table 1.

Table 1: Severe head Injury (GCS 8 or less) Resuscitation Protocol

Prehospital Management and ER ATLS Evaluation
- Emergency diagnostic or therapeutic procedures as indicated
- Prioritizes CABs (circulation, airway, breathing), assessment and treatment

Endotracheal Intubation: Ventilation ($PaCO_2$ 35 - 40 mmHg); Oxygenation (SaO_2 > 90%)
Fluid Resuscitation/Hemodynamics: Maintenance of SBP > 90 mm Hg
Herniation? Deterioration? Rx: ± hyperventilation; Mannitol (0.25-1 g/kg IV)

CT Scan: Surgical lesion → O.R.

Neuro ICU:
- ICP and/or other multimodality monitors
- ICP/CPP management
- Individualized assessment/multi-targeted approach

III. Prehospital Management

The "prehospital guidelines" are accepted as the standard by prehospital and emergency department clinicians.[7] even though; there was insufficient data to support any Level I recommendations for prehospital assessment, treatment, transport, and destination. Therefore, after the guidelines and recommendations were published and implemented, several studies were performed to determine whether or not outcome was improved by following these guidelines.[10, 11, 12, 13, 14] The studies support the direct transfer of patients with severe TBI to a Level I or II trauma center, but controversy remains regarding whether patient outcome is improved by paramedic intubations in the field and mode of transport.[15, 16, 17, 18, 19, 20, 21, 22, 23, 24]

IV. Preanesthetic Assessment and Stabilization

Preanesthetic assessment of the head-injured patient includes: airway (cervical spine), breathing (ventilation and oxygenation), circulatory status, associated injuries, neurological status (Glasgow Coma Scale), preexisting chronic illness, and circumstances of the injury (time of injury, duration of unconsciousness, associated alcohol or drug use).

Secondary insults complicate the course of more than 50% of head-injured patients. An outcome study using data from the Traumatic Coma Data Bank revealed that hypotension after head injury is associated with greater than 70% of patients experiencing significant morbidity and mortality.[4, 25, 26] The combination of hypoxia and hypotension is significantly more detrimental (> 90% of patients with severe outcome or death). We know that hyperglycemia and hypoglycemia can be detrimental to neurosurgical patients. However, currently there is insufficient evidence to support the routine use of tight glycemic control (target BG 80–110 mg/dL) in the operating room or the ICU. [27, 28] The optimal blood glucose level for patients with damaged or injured brain is unknown.

Emergency Therapy. The first step is to secure an open airway and ensure adequate ventilation to prevent secondary injury from hypoxia and hypercarbia.[29] When a cervical spine fracture has not been excluded by radiographic evaluation, intubation should be performed with minimal extension and flexion of the cervical spine, that is, the cervical spine should be maintained in a neutral position during intubation.[30] (Please note that a cadaver study suggests that MILS does not limit movement across a complete $C_{4\text{-}5}$ fracture dislocation with ligamentous injury). If facial fractures and soft tissue edema prevent direct visualization of the larynx, a fiberoptic intubation or intubation with other airway imaging devices may be attempted. In the presence of severe facial and/or laryngeal injuries, a cricothyrotomy may be required. Nasal intubations are avoided in the presence of a suspected basal skull fracture, severe facial fractures, and bleeding diathesis.

Following control of the airway in the head-injured patient, attention should focus on resuscitation of the cardiovascular system. A major concern during fluid resuscitation is the development of cerebral edema. Based on animal research, it appears that the best way to avoid cerebral edema after fluid resuscitation in the injured brain is to maintain normal serum osmolality and colloid oncotic pressure. Therefore, circulating blood volume should be restored to normovolemia with glucose-free isotonic crystalloids and colloid solutions. Glucose-containing solutions are avoided to enhance perioperative glycemic control. Hypertonic saline (HTS) has been proposed as an alternative to normal saline (NS) for fluid resuscitation in patients with hemorrhagic shock and TBI. Controversy continues regarding the selection of the best resuscitation fluids for patients with severe TBI.[31, 32, 33, 34, 35, 36]

A full ATLS trauma evaluation is on-going as therapeutic interventions to control intracranial hypertension are instituted. The head is elevated to 15^0 and maintained in a neutral position. Mannitol (0.25 to 1 g/kg) is administered to acutely lower ICP.[37, 38] Although mannitol is considered the mainstay of hyperosmolar therapy, HTS has gained acceptance as an alternative agent for controlling intracranial hypertension. Neither mannitol or HTS solutions have been associated with improved outcomes.[39, 40, 41, 42, 43, 44, 45] After tracheal intubation, the patient is given a muscle relaxant and mechanically ventilated to a $PaCO_2$ of 35-40 mmHg. Hyperventilation to a $PaCO_2$ of less than 35 mm Hg is avoided unless transtentorial herniation is suspected.[46, 47, 48, 49]

V. Intraoperative Management

Anesthetic Management. In some patients, severe intracranial hypertension precipitates reflex arterial hypertension and bradycardia (Cushing's triad). A reduction in systemic blood pressure in these patients can further aggravate cerebral ischemia by reducing cerebral perfusion pressure (CPP = MAP - ICP). CPP should be maintained between 50 and 70 mm Hg.[50, 51, 52, 53, 54] CPP less than 50 mm Hg should be avoided. The choice of anesthetic agents depends on the condition of the patient. In general, drugs and techniques that reduce intracranial pressure are selected and the overall management goal is to maintain cerebral perfusion and homeostasis.[55, 56, 57, 58, 59] Intraoperative

hypotension secondary to blood loss or precipitated by anesthetic drugs must be avoided by appropriate volume expansion.[51] Maintenance of ventilation ($PaC0_2 \geq$ 35- 40 mm Hg) and oxygenation ($Pa0_2$ > 60 mm Hg) is extremely important.

VI. Postoperative Care/Critical Care.

In the critical care unit (CCU), the main objectives are to enhance recovery from primary brain injury and prevent secondary injury.[60] This requires provision of optimal systemic support for cerebral energy metabolism and adequate CPP, and normalizing of ICP for the injured brain. Prompt recognition and treatment of systemic complications that contribute to secondary injury are essential to head injury management. To achieve this, multimodality systemic and cerebral monitoring should be instituted.[61, 62, 63] Monitoring of ICP, CPP and CBF should be standard practice. In addition, monitors of cerebral oxygenation e.g. jugular bulb oximetry, partial pressure of brain tissue oxygen ($Pbt0_2$), and brain metabolism, have been shown to provide more specific information for managing cerebral hypoxia and ischemia. However, technology has lagged behind in the development of safe, reliable, and continuous cerebral monitors for detecting ischemia.

There is controversy concerning the best management protocol for optimal recovery in TBI patients.[6, 63, 64, 65, 66, 67] A management protocol that uses individualized assessment and a multi-targeted approach to institute therapy and reduce the risk of iatrogenic injuries has gained acceptance.

VII. Summary

The major goal of perioperative management of TBI patients is to prevent secondary damage. Therapeutic measures based on established guidelines and recommendations must be instituted promptly throughout the perioperative course.[68, 69, 70, 71, 72] Recent investigations have shown that not all of the recommended guidelines improve outcome, and more randomized, controlled trials are necessary to clearly address unresolved clinical guidelines.[73] Another challenge for improving metropolitan and regional care of these vulnerable patients is the development of systems and protocols that provide consistent application of the guidelines. There is no doubt that an aggressive approach to managing head-injured patients can reduce mortality, but we must also improve functional status among survivors. Therefore, future studies must focus on all aspects of perioperative care including rehabilitation to reduce disability in survivors.

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Anesthetic Management of Acute Spinal Cord Injury

Name: Deepak Sharma MBBS, MD, DM **City/State Seattle / WA**

Acute spinal cord injury (SCI) is a major public health problem. It occurs with the annual incidence of approximately 54 cases per million in the United States (approximately 17,000 new SCI cases each year). The number of people in the U.S. who are alive in 2017 and have SCI has been estimated to be approximately 285,000 persons. Vehicle crashes are currently the leading cause of injury, followed by falls, acts of violence (primarily gunshot wounds), and sports/recreation activities. Majority (80%) of the reported SCIs occur among males and the average age at injury is 42 years. Most spinal injuries (55%) involve the cervical spinal column and 15% involve the thoracolumbar junction. Incomplete tetraplegia is currently the most frequent neurological category followed by incomplete paraplegia, complete paraplegia, and complete tetraplegia. Less than 1% of persons achieve complete neurological recovery by hospital discharge.

Pathophysiology of SCI

The pathophysiology of SCI is often described as biphasic, consisting of a primary and secondary phase of injury. The primary phase involves the initial direct mechanical injury to the spinal cord, disrupting axons, blood vessels, and cell membranes. This is followed by the secondary injury phase, which evolves over several hours and involves vascular dysfunction, edema, ischemia, excitotoxicity, electrolyte shifts, free radical production, inflammation, and delayed apoptotic cell death. While the primary impact often causes acute neurological damage, the secondary injury results in a progression of neuronal damage over a prolonged period of time. Consequently, the spinal cord edema reaches its' peak 4-6 days after injury.

In addition to the neurologic injury and any associated injuries in patients with polytrauma, cervical and upper thoracic SCI is often associated with cardiopulmonary complications, which impact the anesthetic management. The preoperative evaluation should involve an assessment of these complications:

Neurogenic Shock: Neurogenic shock is a form of distributive shock caused by the interruption of autonomic pathways (loss of sympathetic tone and unopposed vagal tone) where the patients present with hypotension, bradycardia, and hypothermia. Patients with injuries at T4 or higher spinal levels are most likely to be affected by neurogenic shock. Impaired sympathetic tone reduces vascular resistance in large vascular beds resulting in increased venous capacitance, decreased venous return and hypotension. Simultaneous disruption of cardiac sympathetic input allows unopposed vagal activity resulting in bradycardia. Neurogenic shock develops within 30 minutes following injury and may last up to six weeks. It is critical to avoid perioperative hypotension to prevent worsening of secondary injury to the spinal cord.

Arrhythmia: Bradycardia often occurs in patients with SCI. Severe bradycardia usually responds to treatment with atropine but may occasionally require pacing. Heart block, supraventricular / ventricular tachycardia may occur uncommonly.

Autonomic Dysreflexia: Autonomic dysreflexia is a potentially dangerous clinical syndrome that occurs following SCI and often manifests as acute, uncontrolled hypertension. It occurs in individuals with SCI at or above the T6 level. An imbalanced reflex sympathetic discharge following a relatively innocuous stimulus (such as somatic pain, abdominal distention, or bladder distention) leads to potentially life-threatening hypertension which may be complicated by seizures, pulmonary edema, myocardial infarction, or cerebral hemorrhage. Autonomic dysreflexia is more common in the chronic phase after injury, but it can occur in the acute phase as well. It requires immediate treatment by removal of the potential stimulus and pharmacotherapy with vasodilators.

Pulmonary Complications: SCI is often complicated by respiratory failure, pneumonia, atelectasis, pulmonary edema, or pulmonary embolism during the acute phase. High cervical injuries affect the diaphragm and accessory muscles of respiration. The risk of pulmonary complications is higher in patients with cervical SCI. The sympathectomy associated with injuries above T6 may result in bronchospasm and increased pulmonary secretions, which can contribute to mucous plugging and worsening hypoxia.

Gastrointestinal Complications: Mid-high thoracic SCI may cause gastric dilatation, delayed gastric emptying and paralytic ileus which pose the risk of aspiration during anesthetic induction.

Glucose and Electrolyte Imbalance: Hyponatremia after SCI may stem from the renal sympathetic pathways regulating the renin–angiotensin system. Glucose tolerance is often impaired by the stress response. Iatrogenic administration of glucocorticoids may further worsen hyperglycemia.

Temperature Dysregulation: The sympathectomy associated with high SCI can cause vasodilation and heat loss below the level of injury. Patients with neurogenic shock are frequently warm to the touch but hypothermic centrally. Core temperature should be monitored closely in the perioperative period.

Clinical Grading of SCI

The American Spinal Injury Association (ASIA) score (modified from the Frankel classification) is the grading scale routinely used for defining the extent of injury. The assessment consists of bilateral strength assessment of 10 muscle groups and pin-prick discrimination assessment of 28 specific sensory locations. ASIA grade A refers to complete loss of motor and sensory function, whilst ASIA grade E refers to intact motor and sensory function. Grades B, C and D refer to progressively less severe involvement of motor and sensory pathways.

Airway Management in SCI

Airway management is possibly the most critical aspect of perioperative management of patients with diagnosed / suspected cervical SCI. Safe and effective airway management in these patients requires an understanding of the effects of various airway management maneuvers and devices on spinal movement and strategies to minimize it to avoid neurologic worsening.

Mask ventilation can cause significant cervical spine movement. In cadaver studies, chin lift and jaw thrust have been shown to result in more cervical spine displacement and increase in disc space than intubation. However, jaw thrust without chin lift / neck extension causes much less displacement. Given the emergent nature of surgery and considerations for delayed gastric emptying, a rapid sequence induction (RSI) with cricoid pressure is often suggested. However, cricoid pressure may cause distraction, angulation, and translation of the injured spine and should be possibly avoided. The Advanced Trauma Life Support (ATLS) guidelines **recommend d**irect laryngoscopy with manual in-line stabilization (MILS) for emergent tracheal intubation in patients with SCI. MILS reduces cervical movement more effectively than a rigid collar during laryngoscopy. The choice of intubation technique is usually determined by the urgency of situation, expertise of the provider and available resources. In subjects without a cervical injury, direct laryngoscopy causes extension of the cervical spine, mostly at the atlanto-occipital junction, and to a lesser extent at the C1 to C2 joint. The subaxial cervical segments from C4 through C7 are minimally displaced but it generates flexion at the cervico-thoracic junction. Additionally, pressure exerted by the laryngoscope blade is transmitted to the spinal cord. Instability of the occiput–atlas–axis complex may lead to anterior movement of the atlas during direct laryngoscopy, thereby reducing the space available for the spinal cord. While direct laryngoscopy can cause significant spinal movement, at the hand of experienced anesthesiologists, it is often quick, safe and effective in securing the airway. The type of laryngoscope blade (Macintosh or Miller) employed does not appear to significantly affect movement of the spine. The use of a video laryngoscope during MILS allows improved visualization of the glottis with reduction in the degree of cervical spine motion. Fiberoptic intubation causes little motion of the cervical spine. However, coughing or gagging must be avoided to prevent motion of the injured spine. Importantly, no one technique has been proved to be clearly superior to others in the setting of SCI. The cervical collars, notably do not significantly reduce cervical movement during airway management and may in fact obstruct direct / indirect laryngoscopy. Hence, they may be carefully removed prior to intubation once the patient is anesthetized. Supraglottic devices have also been shown to produce significant cervical spine movement but may be essential in life saving difficult airway scenarios particularly where mask ventilation is impossible. While a spine surgery may not be feasible with LMA, the intubating LMA allows subsequent intubation.

Drug choices during airway management are equally critical. Hemodynamic stability and avoidance of hypotension is critical. There are no data demonstrating the superiority of one induction agent over the other and the anesthesiologist should use clinical judgment based on patient characteristics. Succinylcholine may be used safely in the early phase of SCI but should be avoided between 3 days and 9 months following SCI due to the risk of succinylcholine induced hyperkalemia. The availability of suggamadex to rapidly reverse neuromuscular blockade allows rocuronium to be considered as a suitable alternative.

Choice of Anesthetic Agents

Choice of medications for maintenance of anesthesia depends on clinical characteristics specifically the need for intraoperative neurophysiological monitoring, neurological status of the patient and co-morbid conditions. There are no data demonstrating superiority on one anesthetic agent over the other to improve outcomes of SCI.

Hemodynamic and Fluid Management in SCI

Maintenance of hemodynamic stability in the perioperative period is critical because systemic hypotension causing compromised spinal cord perfusion may worsen the secondary neurologic injury. Spinal cord blood flow is autoregulated in the same fashion as cerebral blood flow but may be compromised following SCI. Systemic hypotension may result from hemorrhage and / or neurogenic shock and can lead to cord ischemia. Conversely, an increase in blood pressure leads to significant improvement in axonal function both in the motor and somatosensory tracts of the cord and aggressive goal-directed hemodynamic management may contribute to improved outcome.

American Association of Neurological Surgeons (AANS) recommends maintaining the MAP at 85–90 mmHg and avoiding SBP less than 90 mmHg (Class 3 evidence) for 5-7 days after SCI. Hemodynamic management involves judicious administration of intravenous fluids and vasopressors / inotropes. Most patients after SCI require initial volume resuscitation with crystalloids, followed by albumin and blood products as necessary to avoid fluid overload. A combination of several clinical endpoints other than hemodynamics guide fluid management. These include acid–base status, lactate levels and blood loss. Cervical and upper thoracic spine injuries warrant an agent with inotropic, chronotropic as well as vasoconstrictive properties. Dopamine, norepinephrine, and epinephrine are often useful in this setting. Refractory bradycardia may require treatment with anticholinergic agents or pacemakers.

Spinal instrumentation may involve significant blood loss, which may need to be replaced during surgery. Prevention of severe anemia as well as coagulopathy is critical although there are currently no transfusion triggers specific to patients with SCI. Strategies to reduce intraoperative blood loss and transfusion requirement are important. The use of the Jackson table, where the abdomen hangs free from compression, reduces the vena cava pressure and epidural venous bleeding. Antifibrinolytic agents, particularly tranexamic acid have been shown to decrease intraoperative and perioperative blood loss although the data supporting benefits in terms of transfusion requirements are conflicting. No increase in thromboembolic complications has been reported with the use of traexamic acid in this population.

Intraoperative Neuromonitoring

In order to monitor the integrity of the spinal cord and the nervous structures, intraoperative monitoring of evoked potentials (sensory and motor) and spontaneous electromyography (EMG) is increasingly being used. Somatosensory evoked potentials (SSEP) are elicited by stimulation over peripheral nerves and gauging the response at some point along the sensory pathway, usually at the somatosensory cortex. Motor evoked potential (MEP) monitoring involves transcortical stimulation over the motor cortex and recording the muscle response in the respective muscle groups. Spontaneous EMG activity is recorded by electrode placement in the muscle innervated by the nerve to be monitored. It is particularly useful in monitoring the mechanical irritation of nerve roots. Although intraoperative neuromonitoring is sensitive and specific for detecting neurologic injury during spine surgery, there is a low level of evidence that it actually reduces the rate of new or worsening perioperative neurological deficits.

In addition to the surgical trespass, several additional factors may influence the quality if evoked potential signals. These include anesthetic agents, hemodynamics, temperature, position and technical factors. The anesthetic agents effect SSEPs and MEPs in a drug and dose dependent manner and the effects may vary based on the baseline neurologic function status. The MEPs tend to be most sensitive to the effects of anesthetic agents while SSEPs are somewhat less sensitive and brain stem evoked potentials are most resistant. Volatile anesthetic may be used when SSEPs are being monitored, provided their dosing does not exceed 1 MAC. Volatile anesthetics may also be used for spontaneous EMG recording, provided muscle relaxants are avoided. However, volatile anesthetics and nitrous oxide may be avoided avoided and a total intravenous technique without muscle relaxation used when MEP monitoring is performed, particularly in patients with abnormal baseline function. Dexmedetomidine has been used as an adjunct, with no evidence of detriment to evoked potential monitoring unless a bolus dose is administered. Ketamine is increasingly being used for spine surgery and in addition to other benefits, may allow evoked potential monitoring. A stable anesthesia without significant changes in blood pressure or dosing of anesthetic agents needs should be provided so that changes in evoked responses may be attributed solely to surgical technique.

Corticosteroids:

Methylprednisolone treatment had been suggested in the past to improve neurologic outcomes in patients with acute, non-penetrating SCI. Experimental data showed that the administration of glucocorticoids after SCI reduces edema, prevents intracellular potassium depletion, and improves neurologic recovery when administered early after injury. The National Acute Spinal Cord Injury Study (NASCIS) II trial noted a modest improvement in neurologic function with methylprednisolone administered within eight hours of injury. However, in the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS), patients who suffered a complication were less likely to have received glucocorticoid therapy on presentation than those who did not receive glucocorticoids. Most recently, the American Association of Neurological Surgeons and Congress of Neurological Surgeons have stated that the use of glucocorticoids in acute spinal cord injury is not recommended. Similar position statements / recommendations have been issued by other organizations.

Summary and Conclusion

Successful anesthetic and perioperative management of SCI involves careful considerations of neurologic and non-neurologic manifestations of SCI, adequate planning incorporating judicious airway management and pharmacologic choices, strict avoidance of hypoxia and hypotension, facilitating intraoperative neuromonitoring, strategies to minimize blood loss and avoidance of steroids.

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ICU Management of CNS Trauma

Martin Smith MBBS FRCA FFICM **London, United Kingdom**

The critical care management of traumatic brain injury (TBI) management is based on the central concept that prevention of secondary hypoxic/ischemic injury is associated with improved outcomes. Optimization of cerebral perfusion, oxygenation and metabolic status is therefore fundamental to the management of TBI. Similarly, prevention of further cord injury by early surgery in appropriate patients and optimization of physiologic status is central to the critical care management of traumatic spinal cord injury (tSCI).

TRAUMATIC BRAIN INJURY

Management protocols for TBI have evolved with international consensus, and those from the Brain Trauma Foundation have recently been updated.[1]

Neuromonitoring

TBI initiates a host response which results in a cascade of biochemical, cellular and molecular events that lead to further (secondary) brain injury. Multimodality neuromonitoring provides a comprehensive picture of the (patho) physiology of the injured brain and its response to treatment, and early warning of impending brain hypoxia/ischemia and metabolic distress.[2;3] It allows treatment decisions to be guided by monitored changes in cerebral physiology rather than pre-determined 'one size fits all' targets.[4]

Intracranial pressure and derived indices

Intracranial hypertension is detrimental after TBI. Traditional management approaches have focused on managing ICP and cerebral perfusion pressure (CPP) using generic thresholds for initiation and escalation of treatment, but there is little evidence that ICP-directed management improves clinical outcome.[5] The only randomized study evaluating the utility of ICP monitoring in TBI - the Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure (BEST:TRIP) study - found similar three- and six-month outcomes following treatment guided by ICP monitoring compared to treatment guided by imaging and clinical examination in the absence of ICP monitoring.[6] BEST:TRIP did not test the value of ICP monitoring *per se* but rather the efficacy of the management of intracranial hypertension identified by two different methods. Since both treatment approaches provided satisfactory outcomes despite the absence of ICP monitoring in one, BEST:TRIP challenges the established practice of maintaining ICP below a universal and arbitrary threshold.[7] Individualized interpretation of ICP values in association with other monitored variables, such as autoregulatory reserve, CPP and cerebral oxygenation allows a more rational approach to clinical management.

Recommendations regarding CPP thresholds have varied over time, but current guidance recommends a target of 60 to 70 mmHg and specifically cautions against augmenting CPP above 70 mmHg because of the adverse effects on the lungs of excessive fluid and vasopressor therapy to increase arterial blood pressure (ABP).[1] There is recent interest in the individualized management of CPP guided by assessment of cerebral autoregulatory reserve. Cerebrovascular reactivity, a key component of cerebral autoregulation, is disturbed or abolished after TBI leading to derangements in the relationships between regional cerebral blood flow and metabolic demand and thereby rendering the brain more susceptible to secondary ischemic insults. There are several methods for the continuous monitoring of cerebrovascular reactivity at the bedside and the most established is the pressure reactivity index (PRx) which is calculated as the moving correlation of consecutive time averaged data points of ICP and ABP over a 4-minute period.[8] An inverse correlation between ABP and ICP, indicated by a negative value for PRx, represents normal cerebrovascular reactivity, whereas an increasingly positive PRx defines a continuum of an increasingly non-reactive cerebrovascular circulation when changes in ABP and ICP are in phase. After TBI, cerebrovascular reactivity varies with perfusion pressure and optimizes within a narrow range of CPP specific to an individual. CPP management within this 'optimal' range minimizes the risks of excessive CPP on the one hand and of cerebral hypoperfusion on the other, and is associated with improved patient outcomes in uncontrolled case series.[8]

Cerebral oxygenation

Maintenance of ICP and CPP within established thresholds for normality does not prevent brain hypoxia/ischemia in all patients.[9] Multimodality monitoring incorporating brain tissue partial pressure of oxygen ($PbtO_2$) in addition to

ICP identifies cerebral hypoperfusion more reliably than ICP monitoring alone.[10] $PbtO_2$ values below 10 to 15 mmHg are indicative of ischemia, but low $PbtO_2$ is best considered within a range rather than as an absolute critical threshold and ischemia defined by both duration and depth of hypoxia.[11] Observational studies suggest benefit of supplementing ICP/CPP-guided management with $PbtO_2$-directed therapy to maintain $PbtO_2$ > 15- 20 mmHg, but which intervention or combination of interventions should be used to normalize $PbtO_2$ remains uncertain.[12] The responsiveness of $PbtO_2$ to a given intervention rather than the nature of the intervention appears to be the prognostic factor, with reversal of hypoxia being associated with reduced mortality.[13]

Cerebral microdialysis

Cerebral microdialysis (MD) allows bedside analysis of brain tissue chemistry. Glucose, lactate, pyruvate, lactate:pyruvate ratio (LPR), glycerol and glutamate are measured clinically; each is a marker of a particular cellular process associated with glucose metabolism, hypoxia/ischemia and cellular energy failure.[14] One advantage of MD over other bedside neuromonitoring modalities is its ability to differentiate ischemic and non-ischemic causes of cellular energy dysfunction. Elevated LPR >40 combined with low brain glucose (<0.7-1 mmol/L) suggests severe hypoxia/ischemia and correlates with poor outcome after TBI,[15] but there is no evidence that interventions to normalize brain tissue chemistry are associated with improved outcomes.[14]

Electroencephalography and electrocorticography

Intermittent electroencephalography (EEG) has historically been used for the diagnosis of seizures and status epilepticus, but continuous EEG monitoring is now recommended because of the high incidence of non-convulsive seizures after TBI.[3] Spreading cortical depolarizations are an important mechanism of secondary brain injury, occurring in 50-60% of TBI patients, but are currently only reliably detected via electrode strips placed directly onto the cortical surface.[16]

General principles for the critical care management of traumatic brain injury

The critical care management of TBI patients combines meticulous general intensive care support with interventions targeted to the injured brain; it is important to get the little things right all of the time.[17]

Analgesia and sedation

Adequate sedation is a key component of the management of severe TBI to control ICP and reduce cerebral metabolic demand and tolerance of the injured brain to ischemia.[18] Appropriate and adequate analgesia should be provided with acetaminophen and infusion of opioids.

Cardiovascular and respiratory support

A single episode of hypoxemia (PaO_2 <60 mmHg) or hypotension (systolic BP <90 mmHg) is strongly associated with poor outcomes after severe TBI, and patients with simultaneous hypoxia and hypotension have worse outcomes than those with either insult alone.[19] Brain Trauma Foundation guidelines note that targeting systolic BP $\geq$ 100 mmHg in patients 50 to 69 years of age and $\geq$ 110 mm Hg in those aged 15 to 49 years or older than 70 years may decrease mortality and improve outcomes after TBI.[1] Fluid replacement with isotonic crystalloids to maintain euvolemia is first-line therapy,[20] with addition of vasopressors to augment CPP in the presence of adequate filling.

Patients with severe TBI require airway protection and mechanical ventilation because they are at risk of pulmonary aspiration, compromised respiratory drive/function, and pulmonary complications. Although maintenance of PaO_2 > 60mmHg is essential, increasing FiO_2 beyond that which is necessary to maintain oxygenation targets after TBI is not recommended because of the potential for harm from hyperoxia.[21] Ventilation to normocapnia is recommended to minimize the risk of hyperventilation-associated cerebral ischemia. Short-term moderate hyperventilation may be considered as a temporizing measure to reduce critically elevated ICP, but should be avoided during the first 24 hours after injury when CBF is often critically reduced and always guided by cerebral oxygenation monitoring. Pulmonary complications, particularly pneumonia, are common after TBI and should be treated aggressively. There can be conflict between protective ventilation and brain-directed strategies, and therapy may be a compromise determined on a case-by-case basis.[22] High tidal volume ventilation is a major risk factor for the development of acute lung injury after TBI, and should be avoided.[23] Moderate levels of PEEP ($\leq$15 cmH_2O) do not significantly increase ICP, and may be safely in most patients used as part of a ventilation strategy to optimize PaO_2. Many TBI patients require tracheostomy because of the need for prolonged of mechanical ventilation or airway protection.

There are no randomized clinical trials addressing the optimal timing of tracheostomy but a recent propensity-matched cohort study suggested that early tracheostomy (<8 days) may reduce infection rates, and accelerate weaning and ICU discharge.[24]

Glycemic control

Hyperglycemia (blood glucose >180 mg/dL) exacerbates secondary neuronal injury after TBI and is associated with worse outcomes compared to normoglycemia. However, 'tight' glycemic control with intensive insulin therapy can precipitate cerebral hypoglycemia and metabolic crises.[25] Moderate serum glucose control is therefore recommended, maintaining serum glucose concentration between 125 and 180 mg/dl and avoiding hypoglycemia (serum glucose < 60 mg/dl) and large swings in glucose concentration.[26]

Temperature control

Pyrexia (variably defined as core body temperature exceeding 37.5ºC to 38.5ºC) occurs in more than 50% of critically ill TBI patients and is independently associated with worse outcomes. Causes are multifactorial and include infection and hypothalamic dysfunction. Targeted normothermia is often recommended, but high-quality evidence of outcome benefits is lacking.[27]

Therapeutic hypothermia (TH) has many potential neuroprotective actions including stabilization of the blood-brain barrier, ICP reduction and inhibition of inflammation and intracellular calcium overload. Although several single-center studies have shown benefit, large-scale randomized clinical trials have not confirmed positive outcome effects of TH.[28] A recent randomized controlled trial attempted to control for the heterogeneity of previous studies by inducing TH as soon as possible after injury, maintaining target temperature (32-34˚C) for at least 72 hours, and rewarming slowly (< 1˚C per day), but also found no benefit over fever control.[29] Moderate TH effectively reduces raised ICP and is often incorporated into ICP management protocols (see below).

Anemia

The optimal hemoglobin level to trigger red cell transfusion after TBI has not been defined.[30] A recent randomised controlled trial demonstrated no statistically significant difference in outcome between hemoglobin concentration of 70 vs. 100 $g.l^{-1}$ after TBI, but the higher transfusion threshold was associated more thromboembolic events.[31]

Seizures

Early post-traumatic seizures occur in more than 20% of TBI patients. Although guidelines recommend seven days of antiepileptic drug therapy to reduce the risk of early seizures when treatment benefits are felt to outweigh complications,[1] prophylaxis remains controversial because early post-traumatic seizures have not been associated with worse outcomes. Actual seizures should of course always be treated promptly. There is no role for antiepileptic drugs in the prevention of late posttraumatic seizures. Levetiracetam may have a better safety profile compared to phenytoin which has traditionally been used for seizure prophylaxis and treatment after TBI.[32]

Other supportive measures

TBI is associated with a hypermetabolic state, and early enteral feeding is recommended. A recent meta-analysis found that feeding within 48 hours of admission is associated with reduced rates of mortality, poor outcomes, and infectious complications.[33]

TBI is a significant risk factor for the development of venous thromboembolism. In addition to physical methods of prophylaxis, low molecular weight heparin or low dose unfractionated heparin reduce the rates of deep vein thrombosis (DVT) and mortality respectively. The timing of chemoprophylaxis is controversial but based on evidence from over 5,000 TBI patients it has been recommended that it should be started after 48 h in those at low risk of hematoma expansion and after 72 h in patients at medium or high risk.[34]

Management of intracranial and cerebral perfusion pressures

Guidelines recommend initiation of ICP-lowering therapy when ICP rises above 22 mmHg.[1] Neurocritical care management incorporates tiered ICP-guided strategies administered in a stepwise manner, starting with safer, first-line, interventions while reserving higher risk options for patients with intractable intracranial hypertension, or multimodal neuromonitoring evidence of brain hypoxia/ischemia.[35] The need for treatment escalation reflects more

severe disease and is associated with poorer prognosis; the relative risk of death is increased by 60% if escalation to second tier ICP-lowering interventions is necessary.[36]

Routine, first-tier ICP controlling measures include timely removal of space-occupying traumatic lesions, head elevation to promote cerebral venous drainage and adequate sedation/analgesia. Second tier therapies, such as increasing sedation, osmotic agents and CSF drainage, are indicated if ICP remains > 22 mmHg. Mannitol is recommended by consensus guidelines for the acute treatment of monitored increases in ICP although it has never been subject to a randomized comparison against placebo.[1] Hypertonic saline is also an effective ICP-lowering intervention that is associated with fewer side effects than mannitol, but the superiority of one over the other has not been demonstrated.[37] If second-tier measures fail to control ICP, third tier interventions such as a trial of augmentation of CPP, short-term moderate hyperventilation and TH should be considered. The recent Eurotherm3235 trial which randomized TBI patients with ICP > 20 mmHg resistant to first tier treatments to standard second tier therapy (osmotherapy) or standard care plus hypothermia (32-35ºC) was terminated early because of higher mortality and worse functional outcomes in the hypothermia group.[38] While Eurotherm3235 provides evidence against the early use of hypothermia, it does not address its role in the management of refractory intracranial hypertension.

There are two fourth tier interventions - barbiturates and decompressive craniectomy. Barbiturates have uncertain efficacy in controlling refractory intracranial hypertension, and are associated with serious side effects including cardiac depression, arterial hypotension and increased risk of infection.[39] They should be considered only when other, safer, therapies have been tried and failed, and after careful assessment of the balance between potential benefits (limited) and use-associated risks (high). Decompressive craniectomy is a surgical procedure in which part of the skull is removed and the underlying dura opened in order to reduce brain swelling-related raised ICP. Secondary decompressive craniectomy is most commonly undertaken after TBI as a last-tier intervention in a patient with severe, refractory intracranial hypertension. The RESCUEicp trial demonstrated that decompressive craniectomy was associated with lower mortality but higher rates of vegetative state and severe disability in survivors compared to maximal medical therapy in patients with ICP >25mmHg for >1hr refractory to other interventions.[40]

TRAUMATIC SPINAL CORD INJURY

The critical care management of tSCI is challenging and complex. In addition to motor and sensory deficits tSCI is associated with significant cardiovascular and respiratory disturbances that adversely affect outcomes.[41] Current acute treatment relies on early surgical intervention in appropriate patients,[42] and optimization of systemic physiology in order to minimize the risk of extension of spinal cord injury.[43]

Almost 50% of tSCI patients develop at least two complications which are associated with higher mortality and worse neurologic outcomes.[44] Complications usually develop within the first 10 days after injury, and those with the most severe neurological injuries are most at risk. Critical care monitoring and management allows early detection and treatment of hemodynamic instability, cardiac disturbances, pulmonary dysfunction and hypoxemia, and has led to improved survival and recovery after tSCI.[45]

Respiratory management

Pulmonary complications, including pneumonia, pulmonary aspiration, impaired secretion clearance, pulmonary embolus, and ARDS, are reported in 10% to 60% of tSCI patients,[46] and respiratory failure is the leading cause of death.[47] Pulmonary dysfunction is related to multiple mechanisms including decreased/absent diaphragmatic and intercostal function, bronchoconstriction from loss of sympathetic tone, and weak/paralyzed abdominal muscles preventing effective cough and secretion clearance.

Pneumonia occurs in 60%-70% of patients with complete cervical tSCI and 20%- 30% of those with incomplete injury.[46] Almost 80% of patients with complete injury at C6 or below require intubation and ventilation, and 50% will require tracheostomy.[48] Early tracheostomy (within 7 days) is associated with reduced risk of ventilator associated pneumonia, and shorter duration of mechanical ventilation and ICU length of stay.[49] Diaphragm pacing in tetraplegic patients reduces dependence on positive airway pressure ventilation, and also has possible neuroplasticity effects leading to the development of alternate phrenic neuronal pathways.[50]

In a systematic review of 21 studies including 1263 patients, the incidence of respiratory complications, requirement for tracheostomy and mortality after tSCI were all reduced when care was delivered using a respiratory management protocol.[46] Specifically, the use of a clinical pathway reduced duration of mechanical ventilation and ICU length of stay by 6 days and 6.8 days respectively, and was associated with a 0.4 mortality risk ratio compared to standard care.

Cardiovascular management

Patients with injury above T6 are at highest risk of cardiovascular dysfunction because of loss of sympathetic control and unopposed parasympathetic activity. Cardiovascular complications manifest as hypotension, bradycardia and other arrhythmias, neurogenic shock and autonomic dysreflexia.[44] In an early case series of 50 patients with complete cervical tSCI, 16% had systolic BP <90 mmHg at admission and 82% developed volume-resistant hypotension within the first 7 days after injury.[51] Neurogenic shock can develop rapidly because of profound loss of vascular tone and potential for severe bradycardia.

Hypotension (systolic BP <90 mm Hg) is particularly deleterious and may lead to spinal cord hypoperfusion, worsening neurologic injury and poor outcomes.[44] MAP should be managed between 85 and 90 mm Hg for the first 7 days following injury with intravascular volume resuscitation and addition of vasopressors in volume-resistant hypotension.[52] Norepinephrine appears to be superior to other agents in maintaining spinal cord perfusion.[53] Beyond the hyperacute phase, hypotension may be prevented by the use of abdominal binders and oral vasopressors. Bradycardia should be treated in the usual manner, but cardiac pacing may be required in recurrent or resistant bradycardia.

Similar to management of CPP after TBI, there has been recent interest in individualized management to optimize spinal cord perfusion pressure (SCPP) guided by monitoring intraspinal pressure at the level of injury in addition to MAP.[54] A recent study found that targeting SCPP rather than a generic MAP threshold enhances spinal cord glucose utilization and may be associated with improved neurological recovery.[55]

Other management

Optimization of other physiologic variables including glycemic and temperature management, and optimization of nutrition are key components of the critical care management of tSCI.[43]

Although very high rates of DVT were previously reported, recent data suggest that the incidence is now around 4%, presumably because of increased used of thromboembolic prophylaxis after tSCI. Pulmonary embolus occurs in 1.5% of patients. Mechanical methods of prophylaxis should be provided from admission and pharmacologic prophylaxis started within 72 hours of injury and continued for at least 3 months.[56] An IVC filter should be considered if combined prophylaxis fails or in patients with contraindications to anticoagulation.

Pressure ulcers develop in 30% to 40% of patients after tSCI; early mobilization, frequent turns, specialty beds, and nutritional support are key preventative measures.[57] Gastrointestinal complications, such as impaired gut motility and ileus, are also common because of autonomic imbalance. These are associated with an increased risk of pulmonary aspiration, delayed absorption of enteral feeding and patient discomfort. Urinary tract infection (UTI) is reported in more than 10% of patients, and should be treated with appropriate antibiotics. There is no evidence to support the use of prophylactic antibiotic therapy.[41]

Neuroprotection and neuroregeneration

Several potential neuroprotective interventions have been shown in preclinical models to halt or reduce the secondary injury cascade that follows tSCI, but none have translated into clinical benefit. The most widely studied agent is methylprednisolone, a synthetic corticosteroid that upregulates anti-inflammatory factors, decreases oxidative stress and enhance endogenous cell survival in animal models of tSCI. However, a series of seminal clinical trials - the National Spinal Cord Injury Studies (NASCIS) - confirmed that high-dose methylprednisolone is associated with serious adverse events (including death) that outweigh potential benefits for neurologic recovery.[58] In two trials, a low-dose infusion of methylprednisolone administered within 8 hours of injury showed potential for neurologic improvement and was not associated with adverse events, but risk of bias and imprecision limits

confidence in these findings. Administration of methylprednisolone is therefore not recommended in the treatment of tSCI. Multiple other agents, including riluzole, minocycline, glyburide, magnesium and fibroblast growth factor, that target components of the pathophysiologic cascade or neuroregenerative pathways after tSCI are currently under investigation in clinical trials.[59] Animal models of tSCI have also demonstrated benefit from hypothermia, and a pilot clinical study identified a trend towards neurologic improvement with no increase in complication rates.[51] A phase 3 clinical trial of hypothermia is on-going.

There is also extensive research focusing on improving outcomes after tSCI using stem cells and other adjuvant therapies, including electrical stimulation.[60]

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ANESTHESIOLOGY 2017
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Radiofrequency Ablation for the Treatment of Spine and Musculoskeletal Pain: Understanding the Basic Principles and Clinical Application

David Provenzano, MD
President
Pain Diagnostics and Interventional Care
Pittsburgh, Pennsylvania

Learning Objectives:

As a result of completing this activity, the participant will be able to

- Explain the role of radiofrequency ablation (RFA) for spine and musculoskeletal pain
- Define the electrophysiological principles of radiofrequency lesioning
- Discuss the evidence for the safety and efficacy for radiofrequency treatment of pain
- Define the technical limitations of radiofrequency and methods to modulate lesion size
- Analyze the current level of evidence for radiofrequency treatment of knee pain

Radiofrequency ablation (RFA) is an interventional technique frequently employed for the treatment of specific pain conditions that originate from the axial spine and musculoskeletal system. These common conditions include lumbar and cervical facet syndrome, sacroiliac (SI) joint dysfunction and osteoarthritic knee pain.

To utilize RFA effectively, practitioners must understand the electrophysiological principles and technical aspects to successfully treat the targeted structure and limit the risk of complications. In addition, practitioners should have an in-depth understanding of relevant anatomy and appropriate patient selection to improve procedural outcomes. The purpose of this refresher course is to provide an overview of the utilization of RFA for the treatment of spine conditions. Particular areas to be discussed include the current level of efficacy and safety data and electrophysiological principles of thermal, pulsed, and cooled RFA. The technical limitations of RFA and methods to optimize and modulate lesion size are also described.

General Principles

The ability to ablate specific tissues while limiting destruction to nontargeted tissues is dependent on factors that influence energy delivery and local physiological tissue characteristics. The bioheat equation describes coagulation necrosis.[1]

Bioheat equation

$$\textit{Coagulation necrosis} = (\textit{heat generated} \times \textit{local tissue interactions}) - \textit{heat lost}$$

In a simplified thermal RFA system, three primary factors determine heat generation and the size of the lesion: distance from the active tip, radiofrequency current density, and duration of application of the radiofrequency current.[2] Heat losses that influence RFA include conduction, convection, and low-resistance shunting.

Monopolar and Bipolar Thermal RFA

Thermal RFA involves the use of high-frequency alternating current and results in irreversible cellular damage from focal high temperature tissue heating.[3] Temperature-controlled RFA systems are primarily employed in interventional pain medicine. For monopolar RFA, the high-frequency alternating current flows from the uninsulated active tip into the tissue. The alternating current produces frictional heating in the tissue surrounding the electrode.[2] In RFA, heat flows from the tissue to the cannula.

For conventional RFA, the time of lesioning, tip size, and set temperature all influence the final lesion size. With monopolar RFA, lesions are in the shape of a prolate spheroid with coagulation occurring primarily in the radial direction perpendicular to the long axis of the electrode. Minimal lesioning occurs distal to the tip. Therefore, for monopolar RFA, the cannula should be placed with its shaft parallel to the target nerve.[4,5] When performing monopolar thermal RFA, it is important to understand the maximum tolerable margin of error for placement that is allowed with a specific cannula as well as the radiofrequency settings that will still allow for a lesion to incorporate

the full diameter of the targeted nerve (Figure 1). The monopolar lesion size for interventional pain medicine is small at present, and the radius of the lesion is approximately 1 to 2 times the width of the electrode for a no fluid preinjection set up.[5,6]

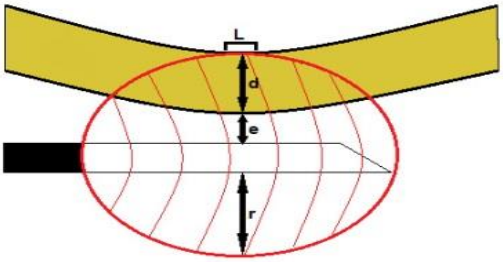

Figure 1. Diagram demonstrating monopolar RF lesioning of a nerve (yellow structure) with an RF cannula. The cannula's active tip is white. The red circle highlights the zone of lesioning. d: diameter of the nerve, e: maximum tolerable margin of error, r: effective radius of lesioning, L: length of nerve lesioned. Figure adapted.[6]

In bipolar RFA, a passive electrode replaces the grounding pad with the goal of focusing the electrical current between the electrodes. A 3-dimensional Cartesian coordinate system describes a bipolar lesion (Figure 2). Bipolar RFA is employed when a larger lesion is required and has been used for SI RFA of the lateral branches.[7-12] When performing bipolar RFA, it is important to understand specific configuration parameters that will influence lesion development including: 1) active tip size and length, 2) fluid preinjection composition, technique and volume, 3) interelectrode distance, 4) lesion time, 5) tip configuration, and 6) tip temperature.[8,10] One parameter that is of crucial importance is the set interelectrode distance (IED). The goal should be to choose an IED that will allow for the ablation of the desired area and minimize destruction to nontargeted structures. In addition, the IED should be set to limit hourglass lesioning. The maximum allowed IED will depend on multiple configuration parameters including the size of the active tip, lesioning time, and composition of the preinjected fluid.[7,8,10]

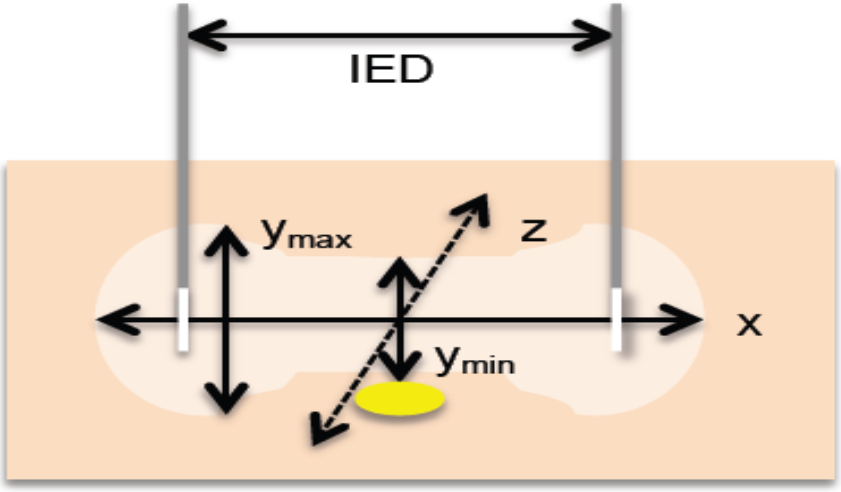

Figure 2. A schematic diagram demonstrating important lesion parameters for a bipolar configuration. x: maximum lesion length, ymax: maximum height, ymin: minimum height, z: maximum depth, IED: set interelectrode distance. The yellow dot represents a nerve that is not being treated secondary to incomplete (hourglass) lesioning in the middle of the lesion in the y-axis. Reprinted with permission.[49]

Cooled RFA

Recently, cooled RFA has been used for the treatment of SI joint dysfunction.[11-13] Compared with traditional thermal RFA, cooled RFA results in significant lesion development distal to the tip of the RFA cannula. Lesioning distal to the tip is advantageous in certain anatomical areas, such as the SI joint, where perpendicular placement of the cannula is often required. In cooled RFA, an electrode is utilized that allows for continuous internal cooling of the tip with a perfusate.[14] The coolant flow rate can be adjusted to modulate lesion size. The internal perfusate serves as a heat sink and removes heat closest to the electrode. The internal cooling allows for greater current deposition which may result in in larger lesions.

Methods to Modulate the Local Tissue Environment to Increase Lesion Size

In the quest to enlarge the coagulation zone, methods to modulate the local tissue environment surrounding the RFA cannula to allow for greater energy deposition have been investigated.[10,14-16] The nerves innervating the facet joints have a diameter of less than 2 mm and anatomical variability is common.[6,17,18] Therefore, the development of controlled and defined larger lesions may assist with lesioning structures that are small and have variable courses, with the goal of limiting technical failures. The chemical composition of the preinjected fluid has been shown to alter lesion size and development in both monopolar and bipolar RFA setups. Increasing the sodium chloride concentration of the preinjected fluid has been shown to significantly increase power output and lesion size.[16,19] Studies to date have been in ex vivo models and further research is warranted. Unlike, monopolar and bipolar RFA, the volume of lesion associated with cooled RFA with interventional pain medicine equipment does not appear to be influenced by the preinjection of small volumes (0.5 ml) of specific fluids.[20]

Pulsed RFA

Pulsed RFA uses brief bursts of radiofrequency energy separated by longer time periods when radiofrequency energy is not applied. The pauses between bursts allow for heat to dissipate within the surrounding tissue. Since the tip temperature does not rise above 42°C, neurodestructive temperatures are not achieved.[21] Although the exact mechanism of pulsed RF is unknown, multiple mechanisms have been proposed. Pulsed RF seems to preferentially target small diameter C and Aδ fibers. In addition, pulsed RF has been shown to alter gene expression in the dorsal horn of the spinal cord, suppress the release of excitatory amino acids in the DRG, attenuate microglial activation in the dorsal horn and enhance the noradrenergic and serotonergic descending pain inhibitory.[22-27] The theoretical appeal of pulsed RFA is the ability to modulate pain without causing the extensive tissue injury seen with thermal RFA.[28] For the treatment of lumbar facet pain, thermal RFA has been shown to be superior to pulsed RFA.[29,30]

Lumbar Medial Branch RFA for Facet Joint Mediated Pain

When performing RFA, it is important to understand the anatomy of the lumbar medial branch and the technical specifications of a radiofrequency lesion.[4,31] As mentioned, the medial branches targeted are small, often less than 2 mm in diameter. Therefore, incorrect needle technique will result in inability to lesion the targeted nerve. Electrodes should be placed parallel to the target nerve.[5]

The therapeutic efficacy of lumbar medial branch RFA has been evaluated in observational and randomized controlled trials (RCTs). Of the six RCTs, three had technical flaws in both patient selection and surgical technique, which hinders interpretation of the results.[32-34] The other three studies had definitively positive results for RFA.[29,35,36] The study by Nath et al.[36] demonstrated that the active treatment groups had statistically significant improvement in back/leg pain and back/hip movement at six months. Improvement was also seen in quality-of-life scores and in reduced use of analgesics. No significant complications were reported. Two observational studies also demonstrated that RFA is effective.[37,38] Dreyfuss et al.,[38] in a study of 15 patients with a diagnosis of lumbar facet syndrome made with diagnostic controlled medial branch blocks, demonstrated 90% pain relief in 60% of treated individuals at 12 months. At least 60% pain reduction was seen in 87% of the patients at 12 months. Gofeld et al.[37], in a large clinical audit of 209 patients (179 of whom completed the study; 35 were lost to follow-up), reported that 68.4% had good (>50% pain relief) to excellent (>80% pain relief) results lasting from 6 to 24 months.

Cervical Medial Branch RFA for Facet Joint Mediated Pain

A systematic review evaluating a randomized controlled trial and four observational studies provides strong evidence that cervical medial branch RFA is a successful treatment for chronic neck pain.[39] Lord et al.,[40] in a

randomized double-blind trial, compared RFA to sham denervation in patients with cervical facet pain confirmed with double-blind, placebo-controlled local anesthetic blocks. RFA denervation was found to be superior to the sham procedure, and the median time that elapsed before pain returned to at least 50% of the preoperative level in the RFA group was 263 days.

SI Joint RFA

Several RFA techniques that target the posterior innervation of the joint have been developed to treat SI joint pain. One of the associated challenges with SI joint RFA includes an incomplete understanding of the innervation of the joint. Furthermore, the innervation of the SI joint consists of small nerves with diameters ranging from 0.292 to 0.997 mm that are difficult to locate with sensory stimulation and have variable anatomic courses in relation to bony anatomy.[41] RFA techniques utilized include bipolar intraarticular RFA, bipolar lateral branch RFA, cooled RFA of the lateral branches, and sensory stimulation guided SI joint RFA.[8,9,11,12,42,43] Recently the employment of cooled RFA has shown promise in the treatment of SI pain. In a randomized placebo-controlled study examining lateral branch radiofrequency denervation with cooled RFA, Cohen et al.[11] reported that 57% of patients obtained 50% or greater pain relief at 6 months. Cooled RFA creates wide diameter lesions that may increase the ability to target areas of nociceptive input. The study by Cohen also demonstrated functional improvements. In individuals with successful pain relief, the median duration of relief was 7.9 ± 4.7 months. Patel et al.[12] studied the efficacy of lateral branch cooled RFA in a randomized placebo-controlled study. Significant improvements in pain, disability, physical function, and quality of life at 3-month follow-up were demonstrated with cooled RFA compared with placebo.

Knee RFA

In a double-blind randomized controlled trial RFA applied to the articular nerves of the knee was examined for the treatment of chronic osteoarthritis knee joint pain in comparison to sham treatment over a 12 week time course.[44] Compared to control, RFA led to significant pain reduction and functional improvement. Following the publication, an editorial questioned the anatomical basis of the described genicular nerves in the manuscript.[45] In an effort to further define the innervation of the anterior capsule of the human knee, dissections of the 8human knees were performed.[46] The dissections revealed 6 nerves: superolateral branch from the vastus lateralis, superomedial branch from the vastus medialis, middle branch from the vastus intermedius, inferolateral branch from the common peroneal nerve, inferior medial branch from the saphenous nerve, and a lateral articular nerve branch from the common peroneal nerve. At least 3 of the nerves were assessable to RFA ablation.

Complications

Although radiofrequency treatment can be associated with both minor and major complications, there are limited data documenting the occurrence of these events.[47,48] Following RFA, a temporary exacerbation of pain secondary to an inflammatory response will often occur and can last several days to two weeks. Lord et al.[6] audited 83 cervical medial branch RFA procedures and recorded procedural side effects and complications. Following cervical medial branch RFA, increasing postoperative pain occurred in 97% of cases with a median duration of 10 days. Some patients may also experience transient dysesthesias of the skin over the operative area, arising from partial denervation of the lateral branch of the posterior primary ramus. These transient dysesthesias occur more frequently with cervical medial branch RFA.

Another concern with RFA is the morphological changes that may occur in the spine after lesioning the medial branches. In the lumbar spine, in addition to providing sensory innervation to the lumbar facet joint, the medial branch also provides innervation to the multifidus muscle. The multifidus muscle plays an important role in segmental spine stabilization and postural stability. Following RFA, electromyography has demonstrated denervation of the multifidus muscle.[49] A recent single cohort retrospective study, suggested that RFA may influence the rate of disc degeneration at treated levels.[50] Validation of this finding is needed in a prospective controlled study.

Other complications that may occur following cervical medial branch and third occipital nerve RFA include ataxia and spatial disorientation.[51] These complications are more common with cervical medial branch RFA of the upper cervical levels, especially the third occipital nerve, and are usually mild and self-limiting.

One of the most feared complications is damage to surrounding nontargeted spinal nerves. Methods to prevent this

complication include precise anatomical placement of the RFA cannula through fluoroscopic guidance, physiological testing, and a detailed understanding of lesion dimensions. The RFA active tips should be positioned safely away from the neuroforamen to avoid thermal lesioning of the spinal nerves. This is especially relevant when methods are used to enhance lesion size, including cooled RFA and fluid preinjection. In addition, the risk of toxicity to nontargeted tissues, including central and peripheral nervous system structures, should be considered prior to injecting specific fluids (i.e., high saline concentrations).[16]

CONCLUSION

RFA is an effective therapeutic treatment for spinal pain originating from cervical and lumbar facet joints and SI joints. In addition, recent research suggests that it may be a promising treatment for osteoarthritic knee joint. Additional work is needed to improve patient selection, extend the duration of relief, and limit technical failures. Furthermore, optimal lesioning algorithms need to be developed which incorporate multiple factors into decision-making.

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State-of-Art Labor Analgesia

Kenneth Nelson, M.D. Winston-Salem, NC

Learning Objectives

As a result of completing this activity, the participant should be able to:

- Utilize the latest technical advances for instrumenting the spinal and epidural spaces
- Apply newer techniques and technologies for maintaining labor analgesia
- Select the most appropriate analgesic agents and adjuncts to use with spinal and epidural techniques

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The options for providing labor analgesia have undergone continuous change over the past few decades, culminating in the current state of the art. Although the available number of topics, issues, and controversies in labor analgesia are nearly unlimited, the current discussion will be confined to three main topics: maintenance of labor analgesia, controversies, and techniques.

MAINTENANCE OF LABOR ANALGESIA

Patient-controlled Epidural Analgesia / Programmed Intermittent Epidural Bolus

Once a catheter has been placed into the epidural space, several options are available to maintain analgesia. One of the first methods to be employed was intermittent bolusing on patient request.[1] Once the effect of the initial dose of local anesthetic began to subside, contraction pain would return and the patient would request more medication, at which time the anesthesiologist would provide analgesia using another bolus dose of local anesthetic. The obvious disadvantage to this technique is the relatively large amount of provider intervention required. Other disadvantages include noncontinuous pain relief and an intermittent increase in side effects such as hypotension and motor blockade owing to bolus doses being larger than infusion rates (or, more accurately, because of high local anesthetic concentrations being used in an attempt to increase duration).[1]

The natural progression in management was to employ infusions to maintain analgesia. Early infusion pumps, however, were relatively primitive, sometimes unreliable, and data were lacking to guide infusion rates.[2] A large volume of research was eventually published to help rectify these problems, and it was during this time that the next step in the evolution of maintenance of labor analgesia occurred: patient-controlled epidural analgesia (PCEA).[3] By this point, copious experience had accumulated with the use of intravenous patient-controlled analgesia (IVPCA), and the same principles were then applied to PCEA. However, some important differences were soon discovered between opioid-based IVPCA for acute postoperative pain and local anesthetic–based PCEA for labor analgesia. Perhaps most importantly, a basal infusion was found to be very

effective with PCEA.[4] Studies continued, and further information has emerged over the past two decades suggesting that even more effective methods can be employed, such as intermittent bolusing at programmed intervals.[5]

Epidural catheters with multiple holes are commonly used to maintain labor analgesia, and "differential flow" occurs through epidural catheters containing multiple holes.[6] During clinically effective continuous infusion rates, the vast majority of flow occurs through the proximal port (Figure 1). Only when pressures become substantially higher will flow begin to occur at the middle and distal holes, which is what occurs during a rapid bolus.[6,7] As expected, analgesia can be improved by employing flow through all three holes. The superiority of programmed intermittent epidural bolusing (PIEB) plus PCEA over continuous infusion plus PCEA has already been demonstrated, and pumps are currently available that are capable of exploiting this advantage.[5,8-10] The concept of differential flow through multiple epidural catheter ports also implies the possibility that different ports can reside in different places (epidural space, subarachnoid space, intravenous) and can cause varying clinical characteristics depending on whether continuous infusion or intermittent bolusing is being used.

The next step in the evolution of maintenance of epidural labor analgesia will be computerized pumps with a feedback loop that can continuously adjust basal infusion rates based on average patient requirements, allowing for automatic changes in infusion rates to match the

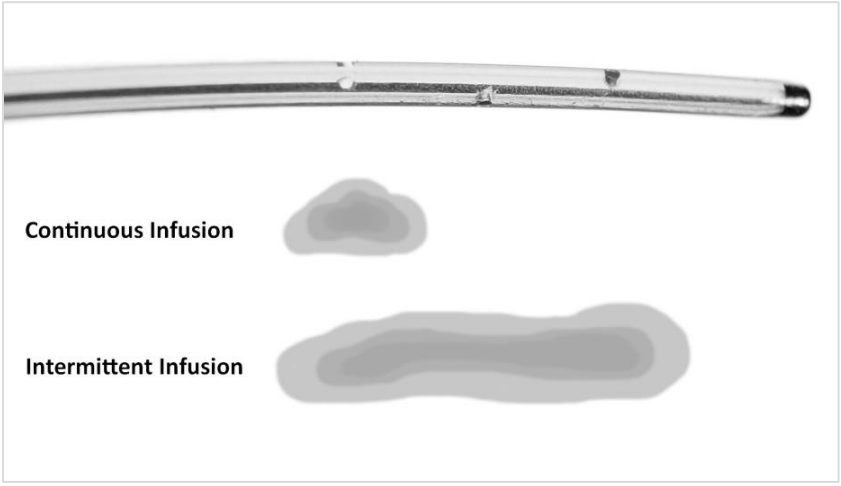

Figure 1. "Differential flow" occurs through a multihole catheter. Continuous infusion at low pressures results in the majority of flow occurring at the proximal port. Only at higher pressures encountered during rapid bolusing will flow occur at the middle and distal holes.

changing analgesic needs during the course of labor. These "smart pumps" are currently under development, and future research will guide the best combination of their use with basal infusions and programmed intermittent bolusing.[11,12]

Intravenous Opioids

There are several acceptable opioids that can be used to provide labor analgesia. Partial agonists such as butorphanol have a ceiling effect for respiratory depression, thus making them an attractive choice in laboring women because of a theoretically lower risk of maternal side effects and neonatal depression.[13] However, the analgesic effect is likewise limited, and analgesic efficacy has been reported to range from moderate to nonexistent. A commonly used dose of butorphanol is 1 mg intravenously every hour as needed, held when delivery is imminent.[14]

Other opioids without ceiling effect have also been used. One of the most commonly studied is meperidine. However, as with all intravenous opioids for labor analgesia, the reported efficacy is variable and often disappointing. One report even concluded that intravenous opioids for labor analgesia are "unethical and medically incorrect,"[15] but the vast majority of studies report at least a moderate effect.[14] Potential drug interactions with meperidine have contributed to its decline in popularity, including serotonin syndrome in patients taking monoamine oxidase inhibitors or selective serotonin uptake inhibitors. Another potential problem with meperidine is accumulation of the metabolite normeperidine, which has been reported to cause convulsions, yet should only be an issue with chronic administration.[16]

Fentanyl is another commonly used intravenous opioid for labor analgesia, and it has been extensively studied for this use. It rarely causes allergic reactions and is relatively free of drug interactions, but has no ceiling effect for respiratory depression and so must be used with caution on the labor ward. It can have a cumulative effect; therefore, neonatal respiratory depression is an important concern.[17] Dosage recommendations are found in Table 1.

Remifentanil is a newer opioid analgesic with a rapid onset and short duration of action. Remifentanil's unique pharmacodynamic profile created early enthusiasm for its use in labor analgesia. However, even with the rapid onset, it is nearly impossible to deliver remifentanil in such a way that the analgesic effect mirrors the time course of the contraction. Doing so would

Table 1. Typical Settings for a Fentanyl IVPCA

Basal rate	None
Bolus dose	25 mcg
Lockout interval	5 min
1-hour limit	300 mcg

IVPCA, *intravenous patient-controlled analgesia.*

Table 2. Typical Settings for a Remifentanil IVPCA

Basal rate	0.025–0.05 mcg/kg/min
Bolus dose	0.25 mcg/kg
Lockout interval	2 min
4-hour limit	3 mg

IVPCA, *intravenous patient-controlled analgesia.*

require remifentanil dosing to occur about 2 minutes prior to the onset of contraction, which is difficult if not impossible to predict. One published study that attempted to provide the remifentanil dose 140 seconds prior to contraction failed to improve labor analgesia.[18] In spite of this shortcoming, there are several reports of remifentanil's successful use in labor analgesia, including a comparison with fentanyl which concluded that both drugs provide moderate analgesia with remifentanil causing more maternal oxygen desaturation and fentanyl causing more neonatal depression.[17] Dosage recommendations for remifentanil are found in Table 2.

Neuraxial Adjuncts

Although epidural labor analgesia relies primarily on local anesthetic agents (and likely will continue to do so in the foreseeable future), a variety of adjuncts have proven to be effective in reducing the amount of local anesthetic required. The common goal of using adjunctive agents is to reduce side effects such as motor block, hypotension, and toxicity by decreasing the amount of local anesthetic required.[19,20] The list of spinal adjuvants that have been studied is extremely long. This discussion will be limited to four: morphine, fentanyl, clonidine, and neostigmine.

Morphine is a very commonly used adjuvant for postoperative analgesia, less so for labor analgesia. It is one of the few spinal adjuvants that have been approved by the U.S. Food and Drug Administration. Although several reports of its use for labor analgesia have shown promising results, its long duration of action means that a longer period of monitoring for respire

tory depression is required.[19] Morphine is also likely to increase the incidence of side effects such as nausea and pruritus.[21]

Fentanyl is a very commonly used adjuvant for labor analgesia because it reduces the amount of local anesthetic required to produce effective analgesia, thereby diminishing side effects such as motor block. The most common side effect is pruritus, and clinically significant respiratory depression is very rare when 20 mcg or less is used.[20]

Clonidine is an alpha-2 agonist that has been shown to be effective in a variety of pain states. Early studies showed it might have promise as an adjunct in labor analgesia,[22] but side effects such as maternal sedation, hypotension, and bradycardia resulted in a black box warning against its use in this setting.[23]

Neostigmine is an inhibitor of the enzyme acetylcholinesterase and therefore causes acetylcholine to remain for a longer period of time in the synapse, thus prolonging its action. Acetylcholine is known to be an important neurotransmitter in the descending inhibitory pathway

initiated by opioid receptor activity in the midbrain, and it is this pathway by which it is believed that neostigmine exerts its analgesic effect. Although intrathecal neostigmine is effective as an analgesic adjunct to local anesthetics, the nausea that it causes is prohibitive to routine use.[24] When used in the epidural space, it is equally effective as fentanyl at reducing bupivacaine requirements, yet does not increase the incidence of nausea.[25] It is currently being used only as an investigational drug, but shows promise in replacing lipid-soluble opioids as an epidural adjunct to local anesthetic, which would eliminate opioid side effects and the need to account for a controlled substance on the labor and delivery ward.

CONTROVERSIES

Air versus Saline for Loss of Resistance

Either air or saline can be safely used to test for loss of resistance when accessing the epidural space. Recent debates on the subject have brought to light the list of reasons to avoid air, whereas no such list exists for the argument against saline.[26] The proponents of air correctly argue that the efficacy and overall incidence of clinically significant morbidities have not been shown to differ between the two techniques, yet case reports and clinical experience have amassed a list of reasons to avoid air. Incomplete analgesia caused by air pockets in the epidural space has been reported in pediatric patients.[27] For the same to occur in obstetrics, it would presumably require large volumes of air, but this is still a potential risk that is avoided by using saline. Venous air embolism[28] and pneumocephalus[29] are more likely to occur with the use of air, and although a small amount of intravenous air is rarely a problem, pneumocephalus is the presumed reason that using air for loss of resistance is more likely to cause headache than using saline. Finally, nerve root compression[30] and subcutaneous emphysema[31] have been suggested as additional potential complications.

One historical argument against saline that is now antiquated, but deserves mention, is the theoretical possibility of confusing saline for cerebrospinal fluid when performing a combined spinal epidural (CSE). In a study comparing air to saline for loss of resistance during the CSE technique, no difference was seen in failure rates and there were no cases of saline being confused for cerebrospinal fluid.[32] This scientific report concurs with what should be expected under these circumstances, in which saline injected into the epidural space distributes among the tissues such as fat and blood vessels and then is not available subsequently to be aspirated through a spinal needle.

Accidental Dural Puncture: What Next?

The risk of accidental dural puncture can be minimized, but not completely eliminated, and carries an overall risk of approximately 1 in 200. Once a puncture occurs, there are two basic management choices that can be made: (1) resite the epidural, or (2) insert a spinal catheter. When choosing a spinal catheter, potential complications to keep in mind include risk of infection,[33] spinal cord trauma,[34] neurotoxicity,[35] and inappropriate injection through the catheter.[36] When choosing to resite an epidural, potential complications include inferior analgesia[37] (compared to a spinal catheter), increased headache risk[38] (also compared to the spinal catheter), and the risk of

unexpected high block.[39] The SCORE (Serious Complications Obstetrics Repository) project has demonstrated that one of the highest-risk scenarios for developing high spinal is when an epidural that is resited after a wet tap is being dosed for surgery.[20] Data are mixed on whether the use of a spinal catheter after wet tap can reduce the incidence of post dural puncture headache, but no study has demonstrated an *increase* in headache risk. Whether choosing a spinal catheter or a resited epidural, perhaps the most important consideration is conspicuous labeling of the catheter at the proximal connector so as to minimize the risk of inappropriate injections.

Nitrous Oxide

The use of nitrous oxide for labor analgesia has a very long history, with its first use for vaginal delivery being reported more than 130 years ago.[40] Even after this great span of time, its use on the modern labor and delivery ward incites controversy, and it is being utilized far more frequently in some geographical areas than in others.[41] Benefits to its use include ease of delivery, noninvasiveness, relative safety, and high satisfaction in some patients. Disadvantages include incomplete analgesia, the requirement for agent delivery and scavenging equipment, and potential adverse effects.[41]

When using the traditional measurement of verbal or visual analog pain scores elicited during labor, nitrous oxide has been shown to provide limited analgesia, especially when compared to neuraxial techniques.[42-44] However, others have shown maternal satisfaction scores after its use to be relatively high.[45] There appears to be a subset of parturients who will benefit from the use of nitrous oxide during labor regardless of its measured effect on reported pain.

To safely deliver and scavenge nitrous oxide, dedicated equipment is required. A mixture of 50% nitrous oxide and 50% oxygen can be delivered by face mask, with an inspiratory valve that prevents gas from escaping the apparatus when the patient is not inhaling. The patient must also exhale into the apparatus to prevent nitrous oxide from escaping into the surrounding environment, whereupon health care workers could potentially be chronically exposed. Although nitrous oxide is a potent greenhouse gas, the overall contribution to greenhouse gas effect from the medical application of nitrous oxide has been estimated to be very low.[46] Maternal side effects are usually minor (most commonly nausea, dizziness, or both),[41] and studies assessing potential adverse effects on the fetus have been reassuring.[47-49]

Experimental animal models of *in utero* exposure to nitrous oxide have demonstrated an acceleration of neuronal apoptosis, but whether this has clinical applicability to the practice of using nitrous oxide for labor analgesia remains to be seen.[50]

For the foreseeable future, nitrous oxide will be a reasonable option for helping parturients cope with the pain and stress of labor, especially those wishing to avoid neuraxial techniques or in whom neuraxial techniques are contraindicated.

Table 3. Typical Drugs Used for Spinal Labor Analgesia with a CSE

Drug	*Dose*	*Volume*
Bupivacaine 0.25%	1.75 mg	0.7 mL

Fentanyl 50 mcg/mL	15 mcg	0.3 mL
Total		**1.0 mL**

CSE, *combined spinal epidural technique.*

TECHNIQUES

Combined Spinal Epidural

Combining spinal analgesia with epidural analgesia was developed as a way of exploiting the attributes of both techniques, *i.e.*, the reliability and fast onset of the spinal combined with the duration and versatility of the epidural.[51] Although the CSE technique is well established, its role in labor analgesia is still being defined. For instance, the use of CSE for patients at high risk for cesarean delivery remains controversial to some because of the "untested" nature of the catheter immediately after placement.[20] Once the spinal analgesic dose is administered and an epidural catheter is placed, it is appropriate to test for spinal placement of the catheter using local anesthetic, but ruling out intravenous placement is more problematic. Furthermore, even if the catheter is appropriately in the epidural space and not intravenous, its functionality for subsequent labor analgesia or unexpected cesarean delivery is unproven. The theoretical concern of higher failure rate and greater morbidity with these untested CSE catheters has not been borne out in studies, but the thought of a STAT cesarean delivery in a morbidly obese preeclamptic parturient with an unfavorable airway and an untested catheter is enough to dissuade many anesthesiologists from using a CSE technique under these circumstances. Intrathecal opioids can also cause pruritus, which is often negligible but sometimes distressing enough to cause patients to request treatment, and even to choose against a CSE with subsequent pregnancies. Nevertheless, the CSE technique has many advantages over the epidural technique alone, including rapid onset, reliability, and minimal motor block.[52] Also, the rate of cervical dilatation has been shown to be enhanced by the use of CSE compared to both epidural[53] and systemic analgesia.[54] One commonly used dosage recommendation is seen in Table 3.

Dural Puncture Epidural

A more recent addition to the obstetric anesthesiologist's toolbox is the "dural puncture epidural."[55] This technique seeks to improve the quality and reliability of epidural analgesia by making a small dural puncture during epidural placement, but without the introduction of spinal medication. Then, the catheter can be fully tested for efficacy while small amounts of the epidural drug pass through the dural puncture to improve efficacy. This technique has been thoroughly investigated and appears to improve analgesia without increasing side effects.[55] Additionally, it addresses the theoretical disadvantage of the CSE technique described above by "proving" the catheter to be fully functional in the event of an unexpected cesarean delivery.

Unintended Catheter "Pullback"

Regardless of the epidural catheter technique used, the timing of securing the catheter to the skin can significantly influence the amount of catheter that remains in the epidural space (Figure 2). When the patient is in the sitting position and flexion of the lumbar spine is optimized, the distance from the skin to the ligamentum flavum is minimized. When the patient returns to a relaxed sitting position, this distance increases and the skin and soft tissues move caudad. Therefore, if the catheter were to be secured to the skin before the patient is allowed to return to a relaxed position, the catheter will be pulled back out of the epidural space by the distance that the soft tissues travel when returning to this position, even as the catheter mark at the skin stays constant.[56] This effect can be further exaggerated by obesity, and can lead to complete failure of the epidural catheter if not recognized. To avoid unintended catheter "pullback," the patient should be allowed to return to a relaxed position before the catheter is secured to the skin. Additional consideration should be given to allowing the patient to lie in the lateral position prior to securing the catheter, as this could allow the soft tissue to move even further, especially in the obese patient.

Ultrasound-guided Neuraxial Block

Advancing technology has made its way onto the labor ward in the form of ultrasound-guided epidural placement.[57,58] Popular for many years in the practice of peripheral nerve blocks, the use of ultrasound has recently seen a flurry of activity in the obstetric anesthesia literature for use in neuraxial procedures. Traditional loss of resistance technique is "blind" in that the anesthe-

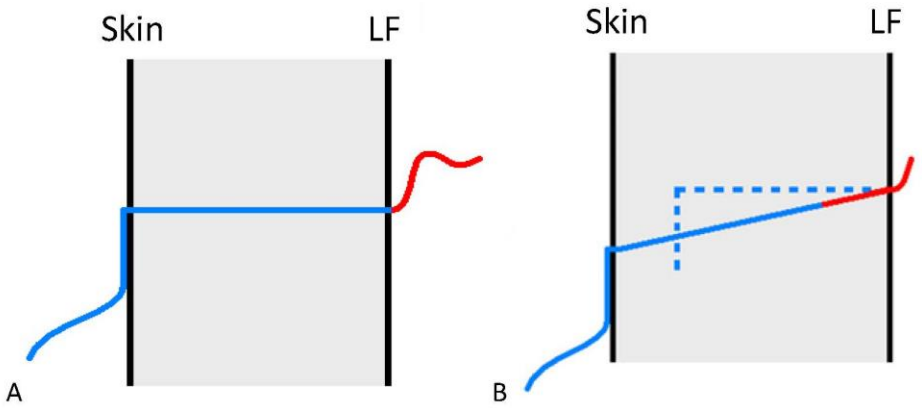

Figure 2. Unintended catheter "pullback" can occur after the epidural catheter is secured to the skin while the patient is still in position for the procedure. (A) With the patient in position for epidural placement, the soft tissue is compressed against the spine. (B) When the patient returns to a natural sitting or lateral position, the soft tissue relaxes and the distance from the skin to the ligamentum flavum *(LF)* increases. If the catheter was secured to the skin while the patient was in the procedural position, then its tip will be withdrawn from the epidural space as the patient resumes a relaxed position. The solid blue/red line represents the epidural catheter, and the dotted line represents the original catheter path.

siologist relies on tactile cues to determine whether the epidural is midline, which tissues the tip of the needle is passing, and when the tip of the needle enters the epidural space. Ultrasonography adds a visual tool that can be used to determine the position of landmarks and to measure depth from the skin surface to the epidural space prior to initiating the procedure. Using ultrasound to guide a neuraxial block in *real time* is more problematic, however, because of the narrow "window" between spinous processes being shared by both the ultrasound probe and the epidural needle.[59]

Proponents of the technique hope that safety will be enhanced with the use of ultrasound. Fortunately, epidural hematoma and infection are extremely rare, and so it will be difficult to ever say conclusively whether the use of ultrasound reduces the incidence of these complications by decreasing the number and duration of attempts required to access the epidural space.[20] Similarly rare is the complication of direct trauma to the spinal cord or conus medularis, but this grave complication can theoretically be avoided by performing the technique below the terminus of the spinal cord.[60] Previous studies have shown that even experienced anesthesiologists are frequently incorrect when predicting interspace level using manual palpation of anatomical landmarks, and when wrong, we are usually higher than predicted.[34,61,62] Ultrasound allows for precise determination of spinal interspace levels, avoiding unnecessary neuraxial procedures above the cauda equina.[62]

Ultrasound remains less ubiquitous on the labor and delivery ward than it is in the peripheral nerve block suite, most likely owing to the perception of a very high rate of success without its use, along with the limitations against its use in real time. Also, the *routine* utilization of ultrasound would result in an increase in the amount of time from patient request to first pain-free contraction, causing some resistance to its use from both the anesthesiologist and the patient.[63] In spite of some limitations, ultrasound is gaining in popularity as a tool for lumbar epidural placement, and in the future is likely to be widely considered an important tool for assisting in lumbar epidural placement in select cases.[64]

Novel Approaches to Locating the Epidural Space

The use of ultrasound waves emanating from the tip of the needle has proven successful for identifying the epidural space in animal models and is expected to reach clinical trials in the future.[65] A similar technology uses optical spectral absorption of the different tissue planes, rather than sound waves.[66] The hope is that someday, our current "blind" approach to the epidural space through loss of resistance will be replaced with advanced technology that allows identification of the tissue planes and epidural space with real-time visualization.

CONCLUSION

What is "State-of-the-Art Labor Analgesia"? The definition is constantly evolving as research and clinical experience guide changes in analgesic agents, neuraxial adjuncts, pumps for maintaining epidural analgesia, and techniques for obtaining access to the epidural and subarachnoid spaces. During this evolution, controversies will inevitably arise, and the anesthesiologist needs to be

aware of the pros and cons of choosing opposing techniques such as air *versus* saline for loss of resistance and whether to place a spinal catheter or resite an epidural following accidental dural puncture. Technology also provides an evolving definition of state of the art as devices are developed and perfected which allow an easier path to the epidural space while minimizing complications.

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ANESTHESIOLOGY 2017
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Update on Pacemakers and ICDs for Anesthesiologists

Eric W. Nelson, DO — **Charleston, SC**
Aman Mahajan, MD, PhD, MBA — **Los Angeles, CA**

Patients with cardiac implantable electronic devices (CIEDs) present for surgery and other interventional procedures with increasing frequency. It is estimated that over 3 million people in the United States have a pacemaker (PM) and more than 300,000 people have an implantable cardioverter-defibrillator (ICD) (1,2). The use of these devices is increasing worldwide. Due to the prevalence of these devices, how quickly the technology advances, and the frequency with which these patients present for procedures, anesthesiologists need to be familiar with how to manage these patients in the perioperative period and also be up to date on new devices.

In 2011 the Heart Rhythm Society (HRS)/American Society of Anesthesiologists (ASA) published an Expert Consensus Statement on the perioperative management of patients with CIEDs. This statement was in collaboration with the American Heart Association, the American College of Cardiology, and the Society of Thoracic Surgeons (3). This article provides information and a guided team approach to this patient population.

The main function of a pacemaker is to prevent bradycardia. Advances in technology, and also understanding of cardiac conduction physiology have led to the development of more physiologic pacing. This includes maintaining the normal atrial ventricular activation over various heart rate ranges, varying the heart rate in response to metabolic demands, and preserving natural ventricular activation.

Standard pacemakers have either 1 (ventricular) or 2 (atrial and ventricular) leads. They are typically implanted for sinus node dysfunction or heart block. A patient is considered to be pacemaker dependent if they suffer significant symptoms or even arrest upon the cessation of pacing (4,5). According to the HRS/ASA Consensus Statement, a pacemaker should be interrogated within 12 months of a procedure. In the perioperative period, necessary information regarding a patient's pacemaker includes the indication, model, programming, batter longevity, lead types, and functionality.

Electromagnetic interference (EMI) is often encountered in the perioperative period and is known to cause malfunctions in pacemakers and defibrillators (6). EMI may affect pacemakers by inhibiting pacing through oversensing, damage at the lead-tissue interface, pulse generator damage, and induction of an electrical reset mode. The most common cause of EMI in the perioperative period in monopolar electrocautery. Bipolar electrocautery because the current is much smaller, however bipolar is much less frequently used than monopolar.

It is important to note that not all patients who are pacemaker dependent need to have their pacemaker programmed to an asynchronous mode for a procedure that may involve EMI. Procedures below the umbilicus typically do not require reprogramming of the device. If the procedure is above the umbilicus and EMI is anticipated, several measures should be performed to ensure patient safety. First, the electrocautery dispersion pad should be placed in such a way so the current from the monopolar tip to the pad does not cross the generator. Second, it is recommended that the device be rendered asynchronous via either reprogramming, or by the placement of a magnet.

Magnets have traditionally been used in the perioperative period to render a pacemaker asynchronous. This is a relatively easy way to render the pacemaker asynchronous, with the added benefit of the device reverting back to its programmed settings once the magnet is removed. It should be noted, however, that the magnet response rate is variable and depends on the device, manufacturer, and individual settings programed by the cardiologist managing the patient and the device.

Also, the asynchronous rate provided by magnet placement may not be appropriate for the patient for a particular procedure. At times, patients require a higher heart rate in order to increase tissue oxygen delivery. To the contrary, most magnet rates are typically above 85 beats per minute, which may not be appropriate for a large subset of patients, i.e. those with aortic stenosis or coronary artery disease. These variables make it important to confirm the magnet effect on each individual patient's device prior to their procedure, and to have an individualized plan for each patient.

The past couple years have seen the advent of a new, leadless pacemaker. Currently, the Medronic Micra is the only leadless pacemaker approved for use in the United States. The Micra is a single chamber device placed in the right ventricle via the femoral vein. Its modes include VVIR, VVI, VOO, and OVO. Because these devices are so new, there is very little data on how to manage these patients in the perioperative period. Due to their small size, these devices do not have a magnet sensor and thus will not respond to a magnet. It is recommended that these devices be reprogrammed to VOO mode to reduce oversensing when EMI is anticipated (7). It should be noted that these devices use the same programmer as their full size counterparts.

Another type of pacemaker that has been increasing in prevalence is a biventricular pacemaker, or cardiac resynchronization therapy (CRT). These devices are indicated in select patients with heart failure, systolic dysfunction, and a prolonged QRS. CRT has been shown to reduce mortality, heart failure symptoms, and also heart failure hospitalizations by synchronizing contraction of the left ventricle. Because of this, patients with CRT should be considered pacemaker dependent due to the constant pacing they undergo to synchronize the ventricle. It should also be noted that these devices may be just a pacemaker (CRT-P), but are more often an ICD as well (CRT-D).

ICDs are implanted in patients for primary or secondary prevention of cardiac arrest. They do this by either pacing out of, or delivering a shock during a ventricular arrhythmia. It is important to remember that all ICDs have the ability to pace a patient, and patients with a CRT-D should be considered pacemaker dependent. Patients with an ICD or CRT should have their device interrogated every 6 months, as they tend to have more comorbidities than patients who have just a pacemaker.

When a magnet is placed on an ICD, it will prevent both defibrillation and antitachycardia pacing. When the magnet is removed, the antiarrhythmia functions will revert back to their programed states. The important thing to remember when using a magnet with an ICD is that it won't do anything to the pacemaker function of the device. That is, if the patient is pacemaker dependent, the magnet will only turn off the antiarrhythmic therapies and the pacemaker will still need to be reprogrammed to an asynchronous mode if EMI is anticipated. If the patient has an ICD, and is also pacemaker dependent, and EMI is expected during the procedure, it is often best to reprogram the device to address both the pacemaker, and the antitachycardia therapy.

A new type of ICD is now on the market and its use continues to grow, the subcutaneous ICD (S-ICD) manufactured by Boston Scientific. This system was initially approved in 2012 as defibrillation therapy and is in use in patients at risk for malignant ventricular arrhythmias who do not have a need for bradycardia pacing, or antitachycardia pacing to manage ventricular tachycardia (8). Although this device is not able to provide long term pacing, it is capable of pacing at 50 pulses per minute for 30 seconds after a defibrillation is given should the patient become profoundly bradycardiac post treatment (9).

The S-ICD consists of a pulse generator and a single subcutaneous lead. Both the pulse generator and the lead are implanted in the subcutaneous tissue and are extra thoracic (10). Currently, the S-ICD can only be implanted in the left chest. The pulse generator is usually implanted between the anterior and mid-axillary lines at the level of the 6th intercostal space. The lead is then tunneled medially from the pulse generator pocket to the xiphoid process and then superiorly along the left parasternal border.

Although different in its makeup, the S-ICD has the same response to a magnet as a traditional ICD. That is, magnet application over the pulse generator will turn off the antiarrhythmic features of the device and removing the magnet will place the device back in its preprogrammed state. A feature the S-ICD has that ensures the magnet is properly positioned is a beeping sound which indicates that arrhythmia detection and shock therapy has been suspended. If the beep is not heard with magnet application, it is recommended that the magnet be repositioned over the device until a beep is elicited.

No matter the type of device a patient has, a team approach should be utilized when caring for a patient with a CIED in the perioperative period. Specific information regarding the patient and their device should be communicated with the surgeon, anesthesiologist, and the CIED team. As stated above, a pacemaker should have an interrogation report within the last 12 months and an ICD or CRT should have a report within the previous 6 months. The device type, manufacturer, and model should be noted along with the indication. Battery longevity, if there were new leads placed within 3 months of the procedure, and the current device programming. Included in this programming it should be noted what the device response to magnet placement is. The team also should note if there are any alerts on the device or the leads and what the pacing and defibrillation thresholds are.

The final piece to management of this subset of patients is the perioperative recommendations. These recommendations may be thought of as a prescription based on the patient, device, and procedure. If the procedure is below the umbilicus, generally the device does not need to be reprogrammed because the risk of EMI is low. For procedures above the umbilicus, ICD tachycardia therapy should be turned off and if the device has a rate responsive feature this should be turned off as well. Patients who are pacemaker dependent should have an asynchronous mode programmed either via reprogramming, or with a magnet if the magnet mode is enabled and the rate is appropriate for the patient and the procedure.

Unfortunately, not all procedure in patients with a CIED are elective. When an emergency procedure presents, there is not always time to engage the CIED team for recommendations or reprogramming. In these instances, it is important to try to ascertain the type of device (ICD vs. CRT vs. Pacemaker). This may be accomplished via a card the patient is carrying, medical records, or a chest radiograph to identify the type of device. Chest radiographs will demonstrate a shocking coil near the distal tip of a ventricular lead in the case of an ICD vs. a pacemaker lead does not have this coil. A CRT device can be identified by a third lead going into the coronary sinus of the heart. An EKG or rhythm strip is helpful in determining if the patient is paced more often than not giving a clue as to pacemaker dependence.

As in nonemergent situations, procedures below the umbilicus typically do not require anything to be done with the device. If the procedure is above the umbilicus, a magnet should be used on an ICD to turn off tachycardia therapy. If monopolar electrocautery is used during the surgery the surgeon should be advised to use short bursts to minimize the risk of oversensing.

Anesthesiologists should have a basic understanding of CIEDs and also the nuances of managing this subset of patients in the perioperative period. As technology continues to change, and as the population lives longer and indications for CIED therapy continues to grow, perioperative physicians will encounter this patient population more frequently. I should also be noted that at times, trained CIED experts (cardiologists, manufacturer representatives) are not available making it the anesthesiologist's duty as a true perioperative physician to be able to fully care for these patients.

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Virtual Cadaver Lab –
Anatomy Pearls in Regional Anesthesia to Improve Clinical Success

David B. Auyong, MD **Seattle, WA**

Key Words:
Regional Anesthesia
Anatomy
Nerve Blocks

Learning objectives:

1) Compare highlighted anatomical structures in photos of fresh tissue dissections to anatomical structures on ultrasound images and videos;
2) Summarize the anatomical relationships of nerves to surrounding structures that facilitate placement of nerve blocks and improve clinical efficacy of regional anesthesia;
3) Examine, at a gross anatomy level, why some nerve blocks are more appropriate than others for specific surgeries of the upper and lower extremity;
4) Recognize anatomic variations in ultrasound images and cadaver dissections and correlate how these variations affect regional anesthesia

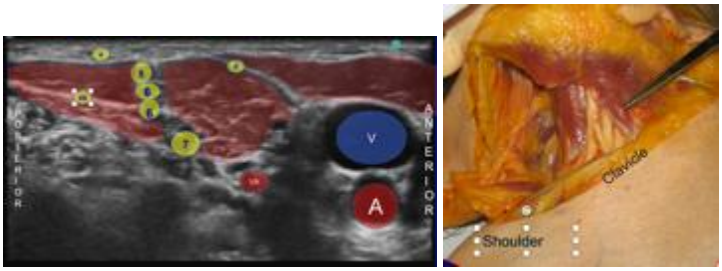
Description:

This lecture covers the anatomical relationships of nerves, vessels, muscle, bone, and skin that form the foundation of regional anesthesia. Images will be presented from multiple dissections in many different fresh tissue cadavers. Unique and clinically relevant correlations will be made between classic anatomical textbook images, the cadaver anatomy and ultrasound images. Anatomical pearls will be reviewed and highlighted for many nerve block approaches to the upper and lower extremity including interscalene, supraclavicular, suprascapular, infraclavicular, axillary, femoral, fascia iliaca, adductor canal, and the sciatic nerve in the subgluteal and popliteal regions. The interplay of gross anatomy and ultrasound images will cement important anatomical relationships, improving clinical success in regional anesthesia. Many oft repeated teachings in regional anesthesia will be explored and then confirmed or refuted by revisiting the gross anatomy of the human body.

Summary:

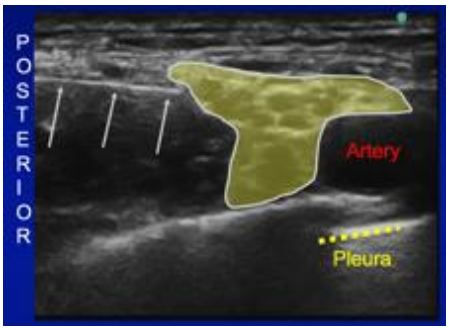
Interscalene Nerve Block

The interscalene nerve block is performed to supply analgesia to the shoulder and clavicle. Anatomical landmarks that can be identified are sternocleidomastoid muscle, anterior/middle scalene, pre-vertebral fascia, roots and trunks of the brachial plexus, vascular landmarks, and specific nerve roots (primarily C5 - monofasicular and C6 – bifasicular). C7 is much deeper. Ultrasound resolution is good enough allowing us to image some of the fascicles that make up the microscopic anatomy of these nerve roots and trunks. Ultrasound does not have the resolution to image all fascicles. Other nerves that can be identified include dorsal scapular, long thoracic, suprascapular, and phrenic.



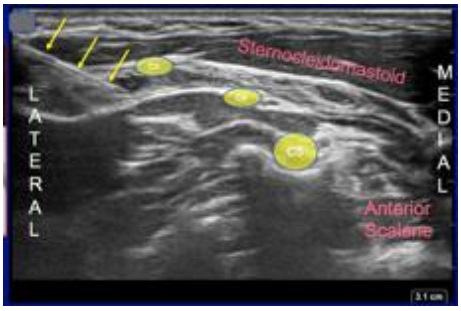
Supraclavicular Nerve Block

Evaluation of the classic image of the supraclavicular nerve block compared to cadaver dissections and microscopic anatomy results in most concluding that this block is usually performed at the level of the trunks. There are three trunks of the brachial with differing emphasis on injection depending on location of the surgery. At this level, the suprascapular nerve is usually quite identifiable and presents a good location for local anesthetic deposition for shoulder surgery. The suprascapular nerve can often be located at the most lateral point of the supraclavicular ultrasound image. For more distal surgery (elbow or lower) the injection at the lower trunk is likely more appropriate.



Cervical Plexus Nerve Block

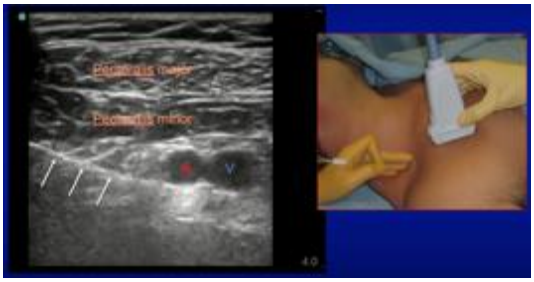
Although previously divided into a deep (muscular) and superficial (skin) nerve block without ultrasound guidance, a complete cervical plexus block can now be easily performed with an injection between the sternocleidomastoid (superficial) and scalene muscles (deep). In subjects that image well, small nerve roots of C2, C3, and C4 can be readily visualized traveling in this plane above the prevertebral fascia.

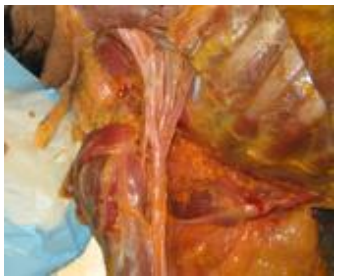


Infraclavicular Nerve Block

The infraclavicular nerve block is significantly facilitated by the Houdini Clavicle maneuver (abducting the arm). This moves the clavicle posterior and allows for a more posterior needle insertion. This posterior needle insertion allows a needle trajectory that is perpendicular to the ultrasound wave propagation and therefore results in a brighter

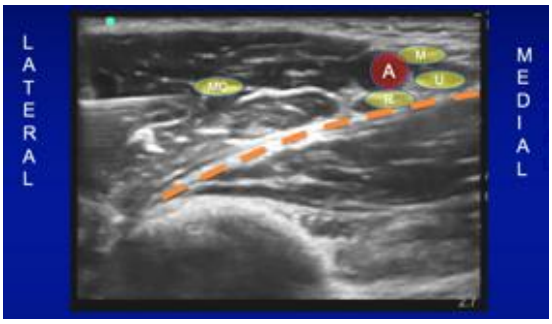
needle image during advancement. This advancement also ensures injection deep to the clavipectoral fascia, a primary barrier to success. Dissections will show significant anatomic variation and the clinical correlate is to place local anesthetic deep to the artery for good success, peri-arterial for optimal success. For safety, needle trajectory should be aimed laterally. A variation is the RAPTIR approach behind the clavicle that can be useful when arm abduction is not possible.





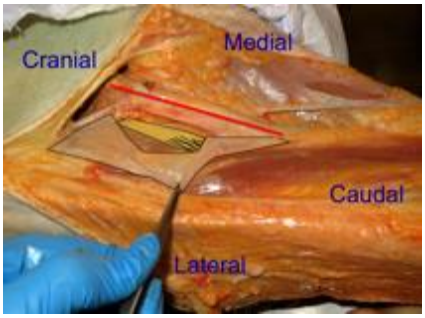
Axillary Nerve Block

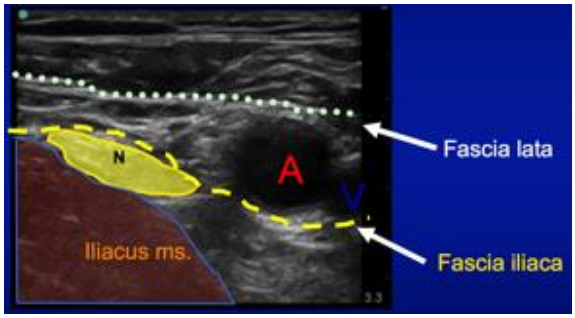
The axillary nerve block is similar to the infraclavicular block in that the nerves, though often described in a classic sense are almost randomly arranged around the axillary artery. In the same patient, nerves can be mobile and found in different places depending on arm, probe position, or probe compression. Most importantly, the "conjoint tendon" is not a tendon but rather a fascial covering. Tendons are terminations of muscles, not covering of muscles. Whatever you want to call it, the fascial covering of the teres major is the perfect anatomic structure to make axillary block reliable. Usually this blocks takes two or three injections: One below, one above, and the musculocutaneous.



Femoral Nerve Block:

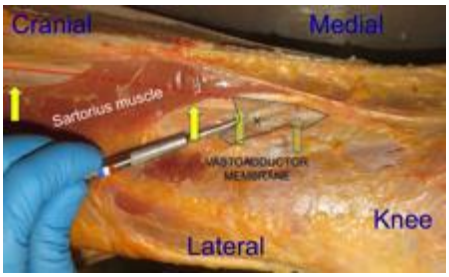
The femoral nerve block is dependent on placement of the local anesthetic under the fascia iliaca. The "triangle" next to the artery is not the femoral nerve. The branch of the femoral nerve that exits to innervate the sartorius muscle exits superficially and therefore is often stimulated with classic stimulator or out-of-plane femoral nerve block approaches. The "fascia iliaca" block is not much different than a properly executed femoral nerve block and likely provides the same clinical effect. A good ultrasound sign of proper injection deep to the fascia iliaca is the spread of local anesthetic underneath the artery. Innervation of the hip joint from the femoral nerve is significant and the branches to the hip capsule exit after the classic area a femoral nerve block is performed. The arteries of the femoral regional provide a perfect road map to identifying the femoral nerve.

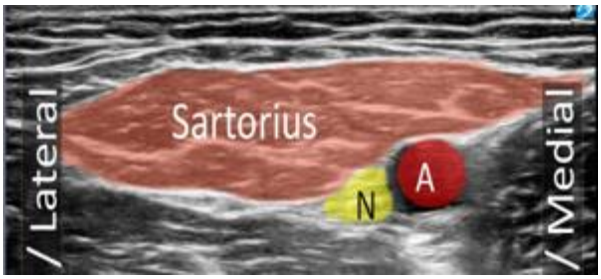




Selective Femoral (Adductor Canal) Nerve Block:

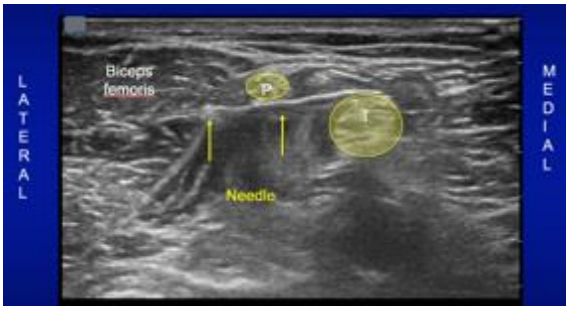
The adductor canal nerve block is performed by identifying the superficial femoral artery in the medial mid-leg. At this level, the sartorius muscle presents an important landmark for placement of the adductor canal block. The sartorius muscle crosses over the artery so the placement of the artery directly under the sartorius muscle is a reliable landmark to ensure the block is not performed too proximal or too distal. The nerves of the adductor canal are reliably found with the artery at this level and are covered with a vasto-adductor membrane. This membrane must be traversed in order to place reliable nerve blocks at this level.





Sciatic, Popliteal

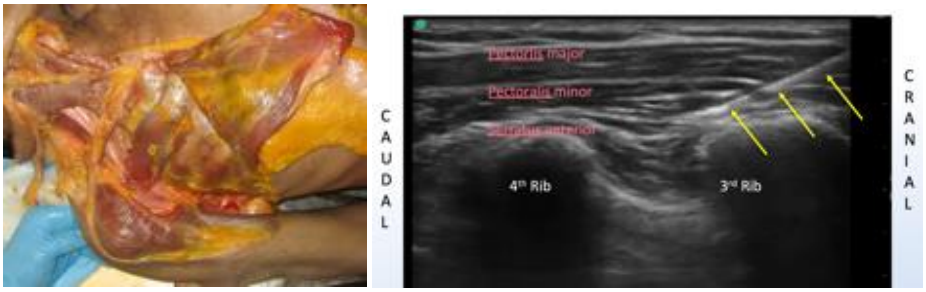
The anatomic relationship of the tibial nerve, artery, and vein at the crease of the knee (snowman) allows the tibial nerve to be easily identified. At this level, the nerves are surrounded in adipose tissue give two clinical correlates: a bayonet artifact may be present with in-plane needle approaches and prolonged nerve blocks may be possible. Clinically, the tibial component (medial and larger) of the sciatic nerve deserves the majority of the local anesthetic resulting in higher quality nerve blocks. Most of the innervation to the knee, leg and foot from the sciatic nerve can be blocked with this approach.



PECS / Serratus Plane

These relatively new nerve blocks have shown promise in providing analgesia for breast, thoracic, and upper abdominal wall surgery or trauma. The key is that these blocks provide nerve block of portions of the brachial plexus that may innervate these areas. There is also thought that local anesthetic deposited in these block locations

may also traverse some of the fascial planes or anesthetize parts of the intercostal nerves. These blocks have been favored over paravertebral blocks as the approaches are usually shallower and further away from the lung, improving ease of placement with ultrasound. Solid evidence for these approaches is still required. Clinically, PECS I is placed between pectoralis major and minor. PECS 2 is placed under or on the lateral border of pectoralis minor. Serratus plane is placed on or underneath the serratus anterior muscle.



Disclosures

FujiFilm SonoSite – Funded Research, Honoraria for Educational Lectures
Halyard Health – Honoraria for Educational Lectures

ANESTHESIOLOGY 2017
BOSTON OCTOBER 21-25

Situational Awareness, Crisis Management, and Patient Safety in Anesthesia Practice

Amanda Burden, MD **Camden, New Jersey**

Learning Objectives

As a result of completing this activity, the participant should be able to:

- Describe Situational Awareness (SA) and Crisis Resource Management (CRM) and discuss their relevance in anesthesia practice
- Outline potential influencing factors that might lead to gaps in SA, even among experienced physicians
- Discuss the significance and potential medical impact of factors affecting CRM
- Discuss strategies to prevent gaps in SA and to implement CRM in daily clinical practice

Author Disclosures

Dr. Burden has reported no relevant financial relationships with commercial interests.

Despite ongoing attempts to improve patient safety, medical errors continue to occur. In 1999, the Institute of Medicine estimated that between 44,000 and 98,000 people in the United States die each year as a result of medical errors.[1] Recent studies have indicated that the true number of premature deaths associated with preventable harm to patients may be far greater, with estimates of more than 400,000 such deaths occurring each year.[2] Many of these deaths are not the result of inadequate medical knowledge and skill; rather, they occur because of problems involving communication and challenges involved with managing the situation and team.[1–6]

The operating room is a dynamic and complex environment; critical events can happen without warning. When these events occur, anesthesiologists must be able to identify, understand, and manage rapidly changing information about the patient and the situation while leading the team. At any time, one or more factors, including patient comorbidity as well as procedural or equipment challenges, may occur in unison and lead to a crisis that threatens the patient's outcome or life.[3–8]

Crisis resource management (CRM), a paradigm first designed to improve aviation safety,[10] was later adapted to anesthesiology by Gaba *et al.* to provide tools that help the anesthesiologist and the team manage a critical situation.[3–8] This Refresher Course module focuses on Situational Awareness (SA), an essential element of CRM. SA was first discussed and studied in aviation and aerospace. In the mid-1990s, Gaba *et al.* wrote that it is equally important in the complex, dynamic, and risky field of anesthesiology.[12] SA is now thought to be one of the most essential nontechnical skills for the achievement of safe anesthesia patient care.[20] As such,

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there is a need for better understanding of SA and the development of new ways to learn about and acquire SA skills in healthcare settings.

HISTORY OF CRISIS RESOURCE MANAGEMENT

Aviation

Crew resource management (originally *cockpit resource management*) is a paradigm that was developed to improve aviation safety by helping flight crews prepare for and resolve crises in flight.[10] Crew resource management training grew out of a National Aeronautics and Space Administration workshop convened to consider data from the National Transportation Safety Board that identified human error and failures of communication, decision-making, and leadership as the primary causes of air transport accidents.[4,10] Crew resource management specifically focuses on interpersonal communication, leadership, and decision-making in the cockpit. Although it retained the pilot's command and leadership of the team, it was intended to foster a less authoritarian culture in which other crew members were encouraged to question the captain (pilot) and offer suggestions for managing a crisis situation.[10]

Crisis Resource Management in Healthcare: Anesthesiology at the Forefront

In 1978, Cooper *et al.* first described the causes of anesthesia-related errors and patient injuries;[3] this early research into error and human factors helped to catalyze a national patient safety movement.[5-9] Cooper's research was one of the influences that led to the formation of the Anesthesia Patient Safety Foundation (APSF), which funded simulation research, specifically the creation of physiological patient simulators.[12-14]

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Inspired by Cooper's research and funded by the APSF, David Gaba and colleagues at Stanford University were the first to recognize that anesthesiology, like fields such as aviation and nuclear energy, is a complex and dynamic environment.[5–9] In part inspired by the book *Normal Accidents*,[15] Gaba began to consider physician decision-making during patient emergencies.[7,9] He adapted crew resource management to the anesthesia environment and called it *anesthesia crisis resource management* (ACRM), as anesthesia professionals would better relate to the concept of crisis management than to "crew" management.[5-9]

CRM skills are difficult to incorporate into clinical practice. To ingrain these behaviors, CRM must be repeatedly practiced in situations that approximate actual conditions under which the behaviors will be used. Beginning in the fall of 1990, Gaba and his group established simulation-based courses to teach these skills to both anesthesia trainees and experienced anesthesiologists.[5-9] Believing that learning is best accomplished when it includes an emotional component, they created as much realism as was reasonably achievable. This team has conducted a variety of CRM courses continuously for the past 25 years. Ultimately, they, along with others, adapted this discipline to other healthcare domains as *crisis resource management* (CRM).[5-9,12-14]

PRINCIPLES OF CRISIS RESOURCE MANAGEMENT

CRM is designed to focus the attention of individuals, and the entire team, on factors that improve patient safety by helping them communicate together and improve their response to

events.[5-9] Although medical knowledge and technical skills are essential components of patient care, nontechnical skills such as leadership, communication, and SA are equally critical for the safe care of the patient, especially during a critical event.[5,6,16]

To manage a crisis effectively, the anesthesiologist must manage the full situation. Gaba describes a set of principles and actions that comprise effective CRM (Figures 1 and 2).[11] These principles consist of actions that focus the team on effective coordination of all activities in response to an evolving event. It is expected that many of these principles (*e.g.*, effective communication) will carry over to routine activities in ways that will make the initiation of an event less likely.[5-9]

Adverse Events in Anesthesiology are Associated with "Human Factors"

The discipline of Human Factors (HF) addresses human behavior, abilities, and limitations, and their relationship to the work environment. HF applies these considerations to the design and evaluation of safer and more effective tools, machines, systems, tasks, jobs, and environments.[13] The issues addressed may be physical, organizational, or even cultural. HF aims to optimize both human and environmental factors to enhance safety.

SA is an essential element of CRM that is well described in the HF literature.[12,13] SA involves perception as well as understanding and integration of information from the dynamic environment into clear decisions and actions; all decision-making and action flows from this awareness. SA involves the anesthesiologist's perception and understanding of the dynamic information that is present in his or her environment. It is also the process of integrating relevant information from the environment into a concise picture. SA includes having awareness of the team as a whole and what other members of the team are doing.[12,16] It is a process the anesthesiologist must work through while she or he quickly detects, integrates, and interprets data gathered from the environment and the resulting knowledge or awareness of the situation.[12-21]

Potential Impact on Patient Safety of Gaps in Situational Awareness

What are the benefits of being able to assess a situation well and having "good situational awareness?" How do you build and maintain adequate SA? What are the risks associated with having an incomplete or even wrong situational assessment and awareness? What can be done to assure adequate SA in a crisis? Is it possible to avoid the pitfalls associated with having inadequate SA?

SA is an everyday occurrence; we use it for routine events like driving. It is also part of more complicated and risky situations (*e.g.*, a physician assessing a potentially septic patient or a pilot assessing the potential for landing gear problems during a final approach). SA involves several cognitive functions such as perceiving, understanding, reasoning, and thinking, all of which influence decisions and actions.[12,16-21] SA is more than perceiving data; it involves integrating that information so the anesthesiologist and team understand what they mean and what is pertinent to the current situation. For example, it requires that the anesthesiologist perceive the appearance of urticaria and concurrent hypotension coinciding with the administration of an antibiotic, comprehending that this may mean the patient is in or is approaching anaphylactic shock, and alerting the surgeon and other members of the team while at the same time treating the patient.

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IMPORTANCE OF SITUATIONAL AWARENESS IN HEALTHCARE

The World Health Organization recently cited SA as critical in all areas of healthcare.[22] Since its origin in the aviation psychology literature, SA is now considered central to safe and effective decision-making and performance in high-hazard areas and domains. Situational and environmental conditions can combine with tasks that are unstable, subject to time pressure, have high stakes, and involve multiple team members. This dynamism and complexity can alter judgments and can impact both individual and team decision-making.[23] Reason stressed the importance of contextual-based decision-making in which the situation and environment are recognized as playing an influential role in the decision-making process.[24] As such, any degradation or loss of SA is very often cited as being associated with environmental or situational conditions, in addition to the more obvious human (individual and team) and performance issues.

The theory of SA is frequently used to explain how decision-makers are able to incorporate information from the environment in a way that allows them to "know what is going on around them" and make critical decisions.[25] Jones and Endsley suggest well-informed decisions require that all relevant elements in the environment are understood.[26] It is also important for decision-makers to understand how these elements interact and impact the situation over time. Endsley suggests that SA can be deconstructed into three levels: *perception, comprehension,* and *projection.*[25] The integration of these three levels is best defined as the "perception of the elements in the environment within a volume of time and space, the comprehension of their meaning, and the projection of their status in the near future."[25]

It is essential to understand what SA is as well as how to achieve it in practice; guidance on how to attain this knowledge and assess the situation is critical.[20,21] This assessment requires understanding the environment and the task, the capabilities and limitations of the team members, and how these factors may affect behavior and performance. There are many factors all of which may ultimately influence the performance of the individual team members and the team as a whole.[1-6]

To analyze a situation involving the many factors that influence performance, start with the basic elements of the situation: the physical and human environments. The *physical environment* includes aspects of the physical space where the situation occurs, the devices, and other conditions such as lighting, noise, temperature, *etc.* The *human environment* includes any other healthcare workers. It also includes organizational aspects such as shift work and handovers, staffing, management and authority gradients, policies, and protocols as well as training and supervision of residents. In addition to the environment, the capabilities and limitations of the individuals or teams must also be considered. All of these issues act together in an interdependent fashion and may produce distractions, interruptions, fatigue, which all add to increased workload, and stress.[22-31]

Establish Situation Awareness and a Shared Mental Model

Anesthesiology is a dynamic process that is accelerated during a crisis.[7] What is correct in the present situation may be wrong the next minute; every piece of information might change during an anesthetic. Some parameters might also change slowly over time. Subtle changes are hard to

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perceive; at times, these cues are barely above the threshold of perception (*e.g.*, small changes in patient vital signs, increased tension among team members in the surgical field, *etc.*).[27]

SA is essential as the patient's condition is continuously reevaluated and potential alternative strategies are considered. Continued investigation is required to assure that the patient's primary problem and the factors that are most likely to cause harm are correctly diagnosed. The anesthesiologist must remain skeptical about the diagnosis, periodically reevaluating other options to recheck the mental model of the situation. After reevaluating the situation, it might be necessary to define new priorities and goals and adapt to the changing environment and to the new situation. New priorities should be clearly communicated to the team, while asking for team members' views.

Strategies to Prevent Gaps in Situational Awareness and Improve Patient Safety

CRM principles are designed to help the anesthesiologist prevent gaps in SA. Ideally, addressing the situation will begin early, before the situation unfolds. In this preliminary and preparatory phase, activities such as briefing and planning should be performed. The preparation phase should be considered as the first critical step in building adequate SA. During this time, as many situational elements as possible can be identified:

Who is the patient?
What do we know about the patient?
Where are we going to treat the patient?
What devices and tools are available?
Who is going to work with me?
What is the procedure we are supposed to perform?
When do we start?
How long has the patient been in this state?

Identifying these points in advance and briefing the team about the patient and the plan before commencing care can help the team prepare to manage the patient.

As the situation unfolds, the key is to build and maintain SA to assure patient safety. Building SA requires continuously scanning the procedure room and the patient to identify what is occurring, understand changes, and think ahead, which enables the anesthesiologist to anticipate and plan for events as they unfold. This cyclical process allows the anesthesiologist to continuously acquire the most up-to-date knowledge so as to eventually implement and, if needed, revise decisions and actions. The process also includes continuing to survey the situation to look for any obstacles to building and maintaining SA. Once the situation is resolved, participants may reflect and debrief on what happened. The process of using CRM principles to continuously maintain awareness of the patient is a crucial tenet of the practice of anesthesiology and allows for safe patient care.

CRISIS RESOURCE MANAGEMENT AND PATIENT SAFETY

Although errors in healthcare have been identified as a leading cause of morbidity and mortality,[1,2] there is no formal required training for healthcare personnel aimed at improving CRM skills. Further, CRM is not yet a standard part of medical training. There is only scant evidence that CRM training improves patient outcomes,[32,33] but practicing for urgent situations

has strong validity on its face. That validity has been sufficient motivation to require such training in aviation and nuclear power. In these arenas, as in healthcare, there is also no level 1 or 2 evidence (randomized trials)[34] that CRM training prevents accidents or saves lives. It is unlikely that this evidence will ever be available, as the lives of pilots and power plant operators are at stake and they are unlikely to volunteer to serve in the control group. As Gaba earlier commented, "…no industry in which human lives depend on the skilled performance of responsible operators has waited for unequivocal proof of the benefits of simulation before embracing it…neither should anesthesiology."[35]

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Building the Best Cardiac Operating Room Team

Lessons in Leadership, Teamwork, and Communication

Jonathan B. Mark, MD
Atilio Barbeito, MD MPH **Durham, North Carolina**

Introduction

More than 510,000 cardiac surgeries are performed annually in the United States.[1] Of those, an estimated 41,000 patients suffer an adverse event, and half of these events are preventable.[2,3] This represents almost 60 complications a day, some of which are devastating. Wound infections, pneumonia, stroke, and procedural injuries represent examples of surgical complications that could sometimes be prevented if cardiac operating room safety were improved.

Several groups, including The Society of Cardiovascular Anesthesiologists through its FOCUS initiative, have identified hazards present in the cardiac operating room (a *hazard* in this context is anything that has the potential to cause an adverse event).[4-9] A common theme that has emerged from this body of work has been the lack of *teamwork*. Wiegmann et al, for example, studied flow disruptions, which represent any occurrence where the normal flow of the operation is interrupted. Teamwork and communication failures, equipment and technology problems, extraneous interruptions, training-related distractions, and issues in resource accessibility could all represent flow disruptions. Surgical errors increased significantly with increases in flow disruptions.[10] Teamwork/communication failures were the strongest predictor of surgical errors. These findings are not surprising, because the care delivered during and around cardiac surgery is an inherently communicative and team-based activity.

What is teamwork and how can we improve it?

Before we define teamwork, it is imperative to clarify the definition of a *team*. A team is 'a small number of people with complementary skills who are committed to a common purpose, set of performance goals, and approach for which they hold themselves mutually accountable.'[11] Teams that are highly specialized and incorporate different professional cultures, are assembled ad hoc, work together for short periods, have dynamic team membership, and have to improvise and coordinate their actions in intense, unpredictable situations are called *action teams*.[12]

Tying a knot during a cardiac operation or performing a trasesophageal echocardiographic exam are examples of tasks that do not constitute teamwork but rather *taskwork*, because they do not require the interaction with other team members. Conversely, the activity of deciding whether or not to return to cardiopulmonary bypass may be considered *teamwork*, because it refers to the interdependent components of performance required to effectively work together to achieve a common goal.[13]

Teamwork then is the multilevel process (and not the product) that arises as team members engage in managing their individual and team-level taskwork and teamwork processes. What does great teamwork look like? What are its attributes? Teamwork includes:

- A concerted physical and mental effort
- Interdependent collaboration
- Shared decision-making[14]

In addition to individuals possessing complimentary knowledge and skills, good teamwork requires certain antecedents:

- Cognition: the team's collective knowledge about the roles, responsibilities, and capability of each member
- Cooperation: refers to collective efficacy (a collective sense of competence), team orientation (a preference for and belief in teamwork, cohesion (a commitment to the team, its task, or both), and mutual trust (a shared belief that all will contribute to and protect the team)
- Communication: communication that is open, adaptable, accurate, and concise

Eight suggestions to improve teamwork

1. *Standardize*

W. Edwards Deming said that 'uncontrolled variation is the enemy of quality'.[15] While he was mostly referring to the manufacturing industry, this is also true around cardiac surgery. Protocols and guidelines have been shown to reduce unnecessary variation and improve patient outcomes.

As an example, our group standardized the OR-to-ICU handover, a process that is repeated daily at the end of each cardiac surgical procedure. In the re-designed handover process, we clearly defined roles and task sequences and structured the transfer of information, taking into consideration local workflow, infrastructure, and personnel constraints (Figure). This effort improved team behaviors and staff satisfaction and reduced clinical workload without increasing handover duration.[16]

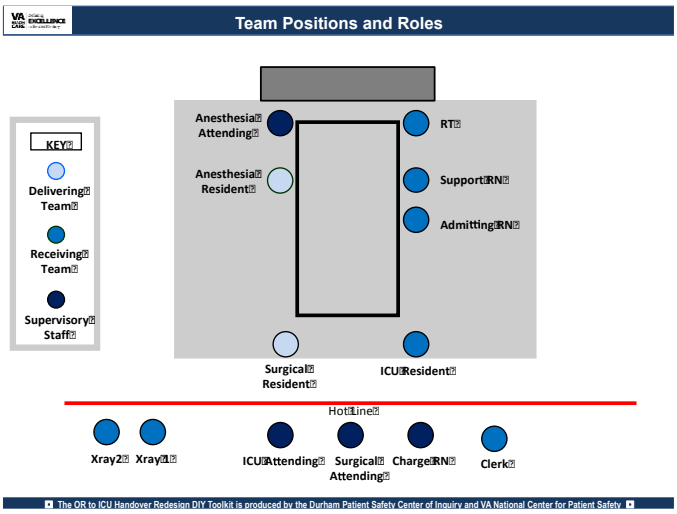

Figure. Example of a standardized OR-to-ICU handover process.
The figure illustrates the standardized position of each member of the surgical (delivering) and critical care (receiving) teams upon arrival in the ICU. Once the physical transfer is completed, the key members of each team move toward the foot of the bed to begin the information transfer portion of the handover in a 'sterile cockpit' environment.

2. *Use human-centered (re) design principles*

Human-centered design (HCD) is a system and product design philosophy that aspires to enhance human abilities, overcome human limitations, and foster acceptance.[17] To achieve these objectives, the system is designed around user characteristics, tasks, and workflows, as opposed to forcing users to change their behavior to accommodate system designs. In HCD, user-centered activities are incorporated throughout the development process, thus allowing users to shape the design of the end product and enhance its usability.[18] The HCD approach has led to significant human-system performance improvements in aviation, military systems, and health care.[19]

We implemented a human-centered approach to the re-design of our postoperative handover process.[16] The change was sustained over time, likely due to the fact that is was designed for and with the end-users.

3. *Use checklists & cognitive aids*

Checklists have been the subject of multiple scientific publications over the past decade. Checklists work by reminding providers to do those things that are easily overlooked in patients undergoing more drastic events. A second effect is to make explicit the minimum expected steps in complex processes – that is, they establish a higher standard of baseline performance. But more importantly, checklists work by also ensuring that providers 'talk and coordinate and accept responsibility while nonetheless being left the power to manage the nuances and unpredictabilities the best that they know how.'[20]

4. *Brief & debrief*

Briefings are semi-structured conversations held by the entire operating room team (anesthesiologists, perfusionists, surgeons, and nursing staff), typically occurring before the patient is brought to the operating room. During a briefing, the team reviews the operative plan, ensuring that each member has a clear understanding of the task at hand so they can plan and anticipate accordingly. Briefings improve efficiency, promote teamwork, mitigate hazards to patients, and reduce preventable harm.[21-23]

Debriefings are held at the end of the case before the team dissipates or at the end of the day, once the surgical list is completed. By reviewing the events of the case (or the day), surgical teams create a space to learn from their own performance. One commonly used format is the plus/delta merhod, where teams discuss (a) what went well, (b) what didn't go well, and (c) what could be done differently next time. Team members often identify creative solutions to problems encountered during the perioperative period, thereby actively engaging in quality improvement.

One study showed that briefings and debriefings increased the sense of team collaboration, reduced staff perception of risk, and reduced communication failures by two thirds.[23]

5. *Train as a team*

Given how fragmented the delivery of medical care is today and how intrinsically team-based the activity is, it is perplexing to reflect on how infrequently we train as teams. Most of the lectures, workshops and simulation exercises that we are exposed to occur in the silos of our own specialties, yet we are expected to function in perfect coordination and cooperation with other disciplines while in the operating room or the ICU.

In this context, training that is conducted jointly with different disciplines and that requires teamwork to complete a task or set of tasks makes sense and has been shown to be effective.[24] One Australian study implemented a brief team-training program on surgical teams and saw a significant improvement in non-technical skills (a set of which include leadership, teamwork and communication) over time.[25] In-situ, simulation-based multidisciplinary training has also been shown to be effective in trauma, perinatal, and other teams.[26,27]

6. *Don't be afraid of conflict*

Effective teams engage in interdependent collaboration to make shared decisions. It is unthinkable that a team could collaborate for an entire day and make difficult decisions in a time-pressured environment such as the cardiac operating room without ever conflicting with one another. In fact, a lack of conflict would be problematic in this setting. Team members that collaborate effectively 'rub against each other', which enhances team bonding by causing those involved to change their attitudes and grow personally. This type of 'healthy conflict' also results in a higher level of problem resolution due to the active involvement of all affected team members.

7. *Measure*

As a team engages in teamwork training activities, it is important to measure progress. Measurements may be used to:

- Provide feedback to learners
- Evaluate the effectiveness of programs
- Demonstrate value to leadership
- Disseminate results

Several tools exist that allow measurement of certain teamwork behaviors. The Anaesthetists' Nontechnical Skills (ANTS), the Nontechnical Skills for Surgeons (NOTSS), and the Oxford Nontechnical Skills (NOTECHS II) are some of the most widely used.[28]

8. *Build a culture of psychological safety*

Although the very notion of teamwork in cardiac surgery suggests a group of professionals working together as peers, very frequently some members of the team have an unusual degree of power or authority relative to other members. Such power discrepancies inhibit the upward flow of information. Those with less power defer to others in order to protect themselves, and teamwork suffers. There are two corollaries to this: (a) the cardiac operating room is a challenging environment where some members of the team will have difficulty speaking up; and (b) the leaders (those with more power) are in a position to address this challenge, building a culture of psychological safety and promoting improved outcomes.[12]

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ANESTHESIOLOGY 2016
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3 steps to improve anesthesia patient medication safety

C. Dean Kurth M.D.
John J. Downes MD Chair
Department Anesthesiology & Critical Care Medicine
The Children's Hospital of Philadelphia
Professor of Anesthesiology and Pediatrics
University of Pennsylvania Perelman School of Medicine

The delivery of anesthesia and practice of perioperative medicine involve the administration of many medications. Safe medication administration requires high reliability for accuracy to the 5 rights: right drug, right patient, right dose, right time, and right route. As the number of medications increases, the probability of failing one of the 5 rights increases. Thus, it is not surprising that medication errors (ME) and adverse drug events (ADE) occur occasionally during the course of perioperative care and anesthesia.

This lecture will describe the 3 steps that you, your department, and your hospital can take to improve anesthesia medication safety.

1. Understand the drug delivery system
2. Define the drug patient safety problem
3. List culture, technologies, and processes that can improve anesthesia drug safety

Step 1. Understand the drug delivery system

The first step is to understand the drug delivery system in anesthesia and the hospital. The delivery of medications consists of 5 components conducted in sequence.

1. Order/Prescription: the drug is ordered
2. Dispense: there is a location to store the drug, diluents, and other ingredients
3. Prepare: the drug is mixed (eg, powder to solution) and put in a container (eg, syringe, bag, pills)
4. Administer: clinician injects the drug into the patient or provides pills for the patient to swallow.
5. Monitor: the clinician checks to determine the effect of the drug

The performance of drug delivery system is evaluated for timeliness, accuracy, safety, and cost. For timeliness and accuracy, it is adherence to the 5 rights. Cost of drug will not be discussed. Safety is assessed through

- Medication error (ME): Failure to complete a required action in the medication delivery system or the use of an incorrect plan or action to achieve the proper patient care.
- Adverse drug event (ADE): Patient harm related to a drug, regardless of whether an error occurred.

The Failure Effect Mode Analysis (FEMA) is a standard methodology to examine the quality and safety performance of a delivery system. Conducting an FEMA on the anesthesia and hospital drug delivery

systems reveals different susceptibilities to ME between the systems (table). Specifically, the anesthesia system does not use as many high reliability processes and technologies as the hospital system and accordingly is particularly susceptible to ME. However, during the past few years, the anesthesia delivery system has begun to deploy these, such as pharmacy pre-mixing medications, sterile hoods, and double checks; anesthesiologists using CPOE and drug bar coding and scanners.

	in-patient		**anesthesia**	
	personnel	technology	personnel	technology
order	MD/NP	CPOE	MD/CRNA	
Dispense	Pharmacy, pharmacist technician	computer, bar code double checks	Anesthesia workstation Pharmacy	Computer bar code robot
Prepare	technician	Robot, bar code, computer	MD/CRNA	
administer	RN	computer, bar code pump guard rails	MD/CRNA	
monitor	RN, MD, NP	bedside monitors, blood, trigger tools	MD/CRNA	anesthesia monitors

Why is the anesthesia drug delivery different from that of the hospital? It boils down to timeliness and cost. During surgery, drug delivery must occur within minutes to respond to surgical and patient changes, whereas during in-patient care, drug delivery may occur within hours as the disease and patient change slowly. Applying the in-patient drug delivery system to the OR would be very costly to meet the necessary timeliness. Given the economics and surgery-patient dynamics, the drug delivery system for anesthesia will remain different than for in-patient care.

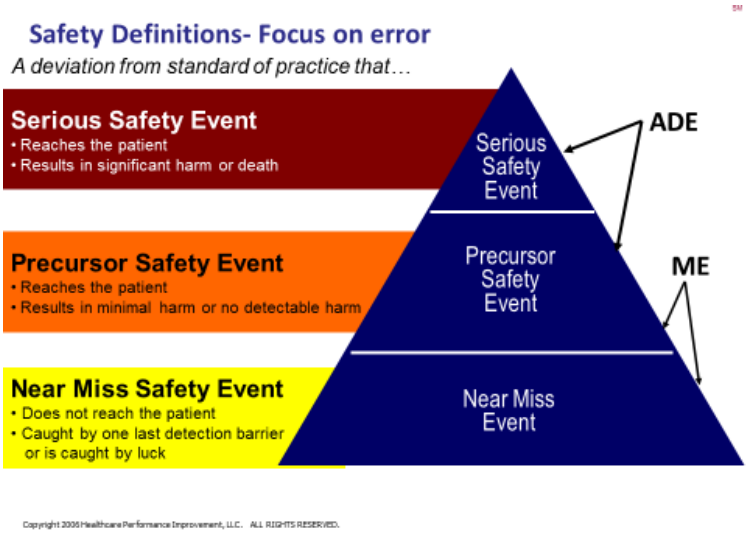
As a result, the anesthesia drug delivery system is susceptible to ME and ADE that the in-patient drug delivery system is not. Although these susceptibilities have been known for many years, improvements have been slow to occur. The second step to improve the system is to define and communicate the problem, to make the case for a "call to action."

2. *Define the drug patient safety problem*

It is useful to review the definitions of event and error before discussing the safety problem.

- Event: unintended occurrence. Events may be further categorized by severity of harm: minor, major, temporary, permanent, or level 1-10.
- Error: unintentional deviation in practice. An error may or may not be associated or causally related to harm.

The FDA defines Serious Adverse events (SAE) as permanent or temporary alteration/loss of physical or mental function. In healthcare, safety events are categorized as Serious Safety Events (SSE), Precursor Events (PE), Near Miss Events NME. The definitions and relationship to ADE and ME are depicted



ADE may be SSE or PE depending on the severity of injury. ADE are categorized level 1-10. SSE are harm level 9-10 and PE harm level 6-8. ME are PE if there was minimal or no detectable harm, and NME if the drug error did not reach the patient. Evident from the triangle, there are more NME than PE than SSE.

Since 2000, 8 studies have identified ME, ADE, and ME+ADE during anesthesia care. The ME+ADE are medication errors that cause harm and represents preventable harm to patients. % per drug is number per 100 drug administrations; % per patient is number per 100 patients. The incidence of ME and ADE varies widely among the studies and is attributable to the study methodology. Nanji used observers in the OR and chart review to identify ME and ADE, whereas the other studies used anesthesiologist self-report. WUS is the patient safety organization for the society for pediatric anesthesia consisting of 30 pediatric anesthesia departments reporting into a registry. On average, the probability of an ADE following a ME is 27%, or about 1 in 5 ME results in significant patient harm.

	ME	ME+ADE	ratio
% per drug			
Nanji 2016	4.10%	1.30%	0.32
Merry 2011	0.33%		
% per patient			
Webster 2001	0.8%	0.2%	0.26
Yamamoto 2008	0.2%	0.02%	0.10
Llewellyn 2009	0.2%	0.02%	0.08
Cooper 2012	0.4%	0.1%	0.37
Kurth 2014		0.02%	
Nanji 2016	55.2%	25.3%	0.46
WUS 2017		0.01%	
average			27%

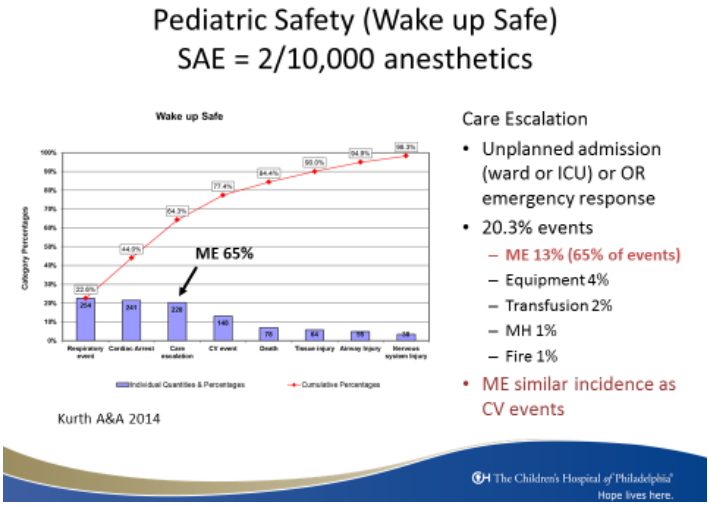
ME can be classified by

- Incorrect dose: Incorrect bolus or rate of infusion of the desired drug administered
- Substitution: Incorrect drug administered instead of intended drug
- Omission: Drug not administered or administered late
- Repetition: Extra dose of intended drug given
- Insertion: Drug administered which was not intended at that time or at any stage
- Incorrect Route: Administered intravenous instead of intramuscular

According to 5 studies in adults and pediatrics conducted since 2000, the majority of ME were incorrect dose, incorrect drug, or not administering the drug. The most common ME were for muscle relaxants, antibiotics, opioids, and infusions due to pump program miscalculation.

error type	Nanji	Cooper	Yamamoto	Abeysekera	Webster	**average**
Incorrect dose	47%	37%	29%	39%	33%	**37%**
Substitution		25%	23%	34%	28%	**27%**
Omission	31%	19%	33%	16%	19%	**25%**
Repetition		15%	0%	2%	11%	**6%**
Insertion	6%	2%	0%	7%	10%	**4%**
Route		0%	10%	0%	3%	**3%**

Despite recognition of ME and ADE for many years, it has been difficult to get a "call to action" in anesthesia departments. The main reason is most ME do not result in patient harm, and the harm rate (ME+ADE) is less common than other anesthesia SAE safety events. In the WUS pediatric registry, ME account for 65% of the SAE care escalation events, defined as unplanned admission to the ward or ICU or OR emergency response. The ME SAE were responsible for 13% of all events, similar to SAE CV events. Thus, in pediatrics, ME represent the fourth most common cause for SAE during anesthesia and surgery.



Given the misperception by anesthesiologists that ME are not harmful, leadership should communicate that in fact they cause harm to get the "call to action" to improve anesthesia drug safety, which brings us to step 3.

3. List culture, technologies, and processes to improve anesthesia drug safety

In 2017, Wahr et al reviewed the literature on anesthesia medication errors and convened an expert panel to formulate recommendations to improve anesthesia drug safety using a modified Delphi process. The expert panel recommended 138 interventions to improve drug safety, with points given for each intervention based on highest probability to improve patient safety. The table displays the top 12 recommendations. The topics of culture, labeling, preparation, and administration ranked highest.

	Topic	recommendation	points
1	culture	High reliability, Reporting & QI systems	190
2	labeling	every drug labeled, pre-printed labels	178
3	administration	read, audio, verify drug	170
4	labeling	every drug color code label	152
5	labeling	standardize drug tray	136
6	labeling	bar code scanner	114
7	preparation	pharmacy- prepares all syringes	104
8	administration	automated alerts antibiotics	96
9	administration	2 person check- non cart drugs	88
10	administration	infusion smart pump libraries with 2 person check	74
11	administration	retain all vials & syringes until end of case	66
12	administration	dangerous drugs not in cart and CPOE to get	62

The expert panel ranked anesthesia culture as #1 topic to improve safety. The culture consisted of high reliability principles, high compliance error reporting by staff, and QI personnel and infrastructure in the department to improve the drug delivery system. Key technologies to improve drug safety included an anesthesia EMR to bar code scan drugs with audio and visual feedback before administration, automated time alerts for timed drugs (eg antibiotics), infusion pumps with smart libraries, and use of CPOE to order dangerous drugs. Key processes included labeling of syringes, pharmacy preparing all syringes, standardizing drug trays in the carts, not keeping infrequently used dangerous drugs in the cart, 2 person checks of dangerous drugs and infusion pump settings, and retaining all vials and syringes until the end of the case to identify errors.

In the only clinical trial to date to evaluate efficacy of these recommendations, Merry et al conducted a prospective open label randomized trial comparing ME between a conventional anesthesia drug delivery system and a new anesthesia drug delivery system employing #2-7 above. The new system decreased the incidence of ME by 20%, indicating some of these recommendations are effective in clinical practice.

Weick and Sutcliff described the principles of high reliability organizations, exemplified by the nuclear power, navy, and aviation industries. High reliability organizations are known for safety. There are 5 features of high reliability organizations involving communication and culture, noted below

High Reliability Organizations

Communication & Culture

1. Pre-occupation with failure
2. Reluctance to simplify interpretations
3. Sensitivity to operations

Prevent

4. Commitment to resilience
5. Deference to expertise

Rescue

Application and embodiment of these 5 features result in organizations preventing errors and adverse events, and if errors and adverse events do occur, the organization can resuscitate the event, resulting in amelioration of injury from the event. Leadership should encourage staff to incorporate these features into their daily work, and build an organization that not only aims to prevent errors and adverse events but also to rescue the patient should an error occur.

ANESTHESIOLOGY 2017
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Leading Articles from Obstetric Anesthesia and Obstetrics Since the Last Annual Meeting

Robert Gaiser, MD
Professor and Chair, Department of Anesthesiology
University of Kentucky

Brenda A. Bucklin, MD
Professor of Anesthesiology
University of Colorado School of Medicine

For this lecture, we have gathered the most recent evidence-based information from various sources to provide an overview of the leading articles from the obstetric and obstetric anesthesia literature.

Antepartum Management

*Non-obstetric surgery during pregn*ancy has been a longstanding concern. The FDA has issued two communications this past year, which had significant implications to the obstetric anesthesiologist. The first was a warning that addressed surgery during pregnancy. This warning discussed the exposure of the pregnant patient in the third trimester to general anesthesia. According to the warning, exposure for more than three hours during the third trimester may affect brain development in the fetus and subsequent newborn. However, the warning also acknowledges that in situations in which surgery is indicated, pregnant women should not delay or avoid surgeries or procedures during pregnancy IF doing so would negatively affect themselves or their infants.[1] The basis for this claim comes from the initial study in 2003 when neonatal rats were exposed to anesthetic agents. These rats had impaired memory acquisition and widespread apoptosis in the developing brain.[2] Subsequent research has established this apoptosis with interference in learning in several different species, including primates. The studies on humans has been varied given the fact that the majority of the literature is retrospective with several confounding variables. The major conclusion from the Pediatric Anesthesia Neuro Development Assessment (PANDA) group is that there is no option for delaying critical surgical procedures in these patients.[3] ACOG also published a committee opinion concerning non-obstetric surgery during pregnancy.[4] The opinion acknowledges that the anesthetic agents do not have a teratogenic effect in humans. Fetal heart monitoring does not have to be continuous rather heart tones should be checked before and after the procedure. The second was a warning about chlorhexidine. According to the FDA, there has been an increase in the number of reports of serious allergic reactions to chlorhexidine with the recommendation that this warning be added to the Drug Facts label. While not FDA approved for skin prep prior to neuraxial anesthesia, the majority of anesthesiologists have switched to chlorhexidine.[5]

Maternal comorbidities

Maternal age of first-time mothers increased 1.4 years from 24.9 in 2000 to 26.3 in 2014. [6] From 2000 to 2014, the proportion of first births to women aged 30-34 rose from 28% (from 16.5% to 21.1%) and first births to women aged 35 and over rose 23% (from 7.4% to 9.1%). The aging maternal population has several implications. In a 10-year study conducted in Washington State, maternal mortality/severe morbidity was examined. Severe maternal morbidity increased exponentially with maternal age over 39 years. Some pre-pregnancy risk factors that increase the risk of morbidity include higher BMI and assisted conception.[7] Sepsis is one of the leading causes of maternal mortality. Interestingly, the risk of sepsis is greater among teen mothers. The diagnosis of sepsis in parturients is difficult. The physiologic changes of pregnancy result in an elevation white blood cell count, heart rate, and respiratory rate. As such, the criteria for SIRS (systemic inflammatory response syndrome) is met in many pregnant women. The diagnosis of SIRS is based upon three of the following four criteria being met: a fever of more than 38°, a heart rate of more than 90 beats per minute, respiratory rate of more than 20 breaths/min, or an abnormal white blood cell count. Sepsis is one of the leading causes of admission to the ICU. In an effort to improve prediction of mortality, the Sepsis in Obstetric Score was designed. This score takes into consideration the physiologic changes of pregnancy. Unfortunately, its ability to predict mortality was no better than other scores. Others etiologies include hypertensive disorders of pregnancy and massive hemorrhage. The ability to predict mortality in the ICU has depended upon the APACHE II score (Acute Physiology and Chronic

Health Evaluation II). In a systematic review of the literature, the APACHE II score consistently overestimated mortality risks for pregnant and recently pregnant women receiving critical care.[8] This point is important given that ICU admission complicates 0.48% of deliveries and pregnant/recently pregnant women account for 1.49% of ICU admissions.

Thrombocytopenia is often associated with pregnancies complicated by preeclampsia. A recent randomized controlled trial examined the impact of high-dose methylprednisolone in preventing a decline in platelets in women presenting with preeclampsia when platelet counts were between 50 and 150 X 109/L.[9] The primary outcome of the study was the proportion of women with platelet counts of >100 X109/L at 36 hours after the first administration of medication. The study included 36 patients who received methylprednisolone and 34 who received placebo. The groups did not differ in the proportion of patients who were thrombocytopenic at 36 hours (83% vs. 85%), nor did they differ in the proportion of patients who received neuraxial anesthesia.

Preeclampsia is characterized by sudden-onset hypertension and proteinuria after 20 weeks' gestation. Clinical observations suggest that early detection and monitoring are beneficial.[10] However, reliable predictors of the diagnosis of preeclampsia have been elusive. Our current understanding is that the ratio of soluble fms-like tyrosine kinase 1 (sFlt-1) to placental growth factor (PlGF) is elevated in pregnant women prior to the clinical onset of preeclampsia. However, this ratio as a predictive value in women with suspected preeclampsia is less clear. Recently, Zeisler et al. [11] performed a multicenter, prospective, observational study to determine if a blood test would help clinicians determine if a patient could be followed safely as an outpatient since many patients are admitted for monitoring to rule out preeclampsia. Five hundred women were followed and their sFlt-1:PIFG ratios were measured between 24 and 37 weeks' gestation. In the study, 38 was identified as an sFlt-1:PlGF ratio cutoff, suggesting that in women with a ratio less that 38, there is a short-term absence of preeclampsia when preeclampsia is otherwise suspected clinically.

Cases of complex congenital heart disease have become more common on labor and delivery. The majority of girls born with congenital heart disease will reach childbearing age. Mothers with congenital heart disease have a higher frequency of spontaneous abortion, higher frequency of recurrence of CHD in the neonate, higher preterm birth rate, and higher perinatal mortality. Significant arrhythmias are common during pregnancy in these patients. Recurrence rate is approximately 50% for those with a history of atrial fibrillation and 25% in those with a history of ventricular tachycardia.[12]

Marijuana is the most commonly used illicit drug during pregnancy with rates varying from 2-28%.[13] Besides increased interest for recreational use, women are also using marijuana to treat nausea and vomiting associated with pregnancy.[14] Although more states are legalizing marijuana, studies evaluating marijuana use during pregnancy are often confounded with recall bias and reporting issues. In addition, those who use marijuana often use other drugs. To evaluate maternal marijuana use and potential adverse effects on pregnancy outcomes, as well as neonatal morbidity, Metz et al. evaluated data from the Stillbirth Collaborative Research Network.[15] Of 1996 live-born controls, 1610 live-born controls were included in the final analysis. Maternal marijuana was identified in 2.7% of births with 1.6% self-reporting. In the study, there were no adverse pregnancy outcomes (small for gestational age, spontaneous preterm birth, hypertensive disorders of pregnancy) independent of tobacco use. However, there was associated composite neonatal morbidity or death (adjusted odds ratio, 3.11; 95% confidence interval, 1.40–6.91).

Opioid-related deaths in women have increased 5-fold over the last decade. Because opioids are commonly prescribed for post-cesarean pain management, Bateman et al.[16] evaluated the risk of persistent opioid use in the year following cesarean delivery in otherwise opioid-naïve women. The authors used a database of commercial insurance beneficiaries and identified study subjects who were opioid-naïve and who had undergone cesarean delivery. Approximately 1 in 300 patients became persistent opioid users. Risk factors for persistent use included preexisting psychiatric disease, pain conditions, and substance use/abuse. More recently a study evaluated more than 160,000 women enrolled in Medicaid in Pennsylvania in order to estimate the prevalence of opioid prescriptions that had been filled after delivery. The authors assessed the number of filled prescriptions or prescriptions filled after pain-inducing procedures. Twelve percent of the women filled an outpatient prescription within 5 days of vaginal delivery. The authors urged national guidelines for prescribing opioids following

obstetric procedures. Recommendations for patients with opioid dependence include: 1) Antepartum anesthesia consultation to establish rapport and obtain an accurate alcohol and substance abuse history as well as to discuss options for analgesia. 2) Early neuraxial analgesia with opioids with continuation of baseline oral opioid maintenance. 3) Postoperative pain control with neuraxial morphine, continuous epidural infusion, acetaminophen, ketorolac or ibuprofen, wound infiltration or PainBuster® continuous wound catheter, and/or TAP blocks.

Labor and Delivery: Obstetric Management

Second stage of labor is defined as the time period from complete cervical dilation to delivery of the neonate. There has been debate in the obstetric community as how to the best management of the second stage. Some individuals advocate for the immediate initiation of pushing once the mother becomes complete while others advocate for delayed pushing in which the mother rests for a time period before initiating bearing down. There has been a trend to allowing the parturient to delay pushing after complete dilation of the cervix. A secondary analysis of deliveries from 2008 to 2011 was conducted.[17] The study participants included 21,034 women who delivered in 25 U.S. hospitals. Of these women, 18.4% delayed pushing. Delayed pushing was associated with second stage beginning during the day and in hospitals with dedicated 24-hour obstetric anesthesia. The difference in the duration of second stage was approximately 2 hours. It also was associated with increased odds of cesarean delivery and of postpartum hemorrhage.

Vacuum extraction is another area of obstetric practice where there were several publications published during the past year. A vacuum is a suction device that is placed on the fetal head and is used in the management of the second stage of labor. Complications of vacuum delivery to the neonate include laceration, cephalohematoma, hyperbilirubinemia, and intracranial hemorrhage. In a study of 7733 vacuum attempts, 96.9% were successful deliveries while 245 were failed vacuum extractions requiring cesarean delivery.[18] Vacuum delivery was not associated with increased risk of neurologic morbidity. Although not statistically significant (p=0.08), there was a greater incidence of cerebral palsy in the failed vacuum delivery group. While the Closed Claims Study has provided information on complications that will result in lawsuit in anesthesiology, similar studies have not been conducted in other specialties. A recent study examined the trends in malpractice claims for obstetric and gynecologic procedures. Over a ten-year period, there were 10,915 claims reported to 20 insurance companies. The majority of the claims (60%) were withdrawn or dismissed. The procedure associated with the highest proportion of paid claims in obstetrics was vacuum delivery. Obstetrics had the second highest average indemnity payment (neurosurgery ranked #1 and anesthesiology ranked #5) and the fifth highest paid-to-closed ratio of all medical specialties.[19]

Labor analgesia is requested by many women for pain relief during labor and delivery. Although over the last three decades, increasing numbers of women utilize neuraxial analgesia for labor, other pharmacologic and non-pharmacologic interventions are common.[20]

Patients desire information concerning labor analgesia. The difficulty is when to provide this information. While the patient is experiencing the labor pain, certain information may not be remembered because of pain. However, all studies indicated that laboring patients are able to recall and to understand information presented to them when experiencing the pain of labor.[21] However, not all anesthesiologists are good at providing information. In an article in *Cosmopolitan*, a patient presented her experience with a post-dural puncture headache.[22] She was not upset about the accidental dural puncture, rather the lack of information of the risk of a headache and that there was a treatment option for the headache. In a qualitative study of women who delivered at a major academic center, access to information was assessed.[23] Women prefer to have their information antepartum and to receive the information from the obstetric provider with whom they have a relationship. The majority of information about labor analgesia was obtained from the internet without any consideration to the content or to the quality.

NPO status during labor and delivery remains controversial. The guidelines for obstetric anesthesia are very clear: oral intake of moderate amounts of clear liquids during labor with clear liquids up to 2 hours before induction of anesthesia. Solid foods should be avoided in laboring patients.[24] Yet, a systematic review was conducted examining less restrictive food intake during labor.[25] In this review of 10 studies which included 3,982 patients,

there were no cases of aspiration. There was only one trial that allowed unrestrictive food intake while the rest of the studies used some form of liquid drink. In the study of unrestrictive food intake, the duration of labor was shorter by 16 minutes. While this study does not endorse the intake of solid materials during labor, it addresses the fact that women continue to be troubled by the policy concerning solid food. There may be some benefit to considering solid intake in low risk parturients. In a study of hospitals across Canada, oral intake was restricted to clear fluids (51%) or solid food (38.1%) as long as the parturient did not have epidural analgesia. When epidural analgesia was used, oral intake was restricted to clear fluids (82.8%) or solid food (7.2%), In 77.5% of hospitals, oral intake during active labor with epidural analgesia was limited to clear fluids and the patient did not receive parenteral dextrose.[26]

Combined spinal epidural analgesia (CSE) has become a commonly used neuraxial technique over the past two decades because of advantages over traditional epidural analgesia: 1) faster onset; 2) better pain scores during the 1st stage of labor; 3) fewer top-ups by the anesthesiologist; 4) confirmation of correct placement; facilitates ambulation. Despite these advantages, questions remain about delayed recognition of a failed epidural catheter because there is concern that the technique is more complicated than either spinal or epidural alone and the epidural catheter is "unproven" during the duration of spinal analgesia. A recent retrospective analysis of ~2400 neuraxial labor analgesics compared CSE to traditional labor epidural analgesia in order to determine whether detection of catheter failure was delayed by placement of CSE.[27] In the study, CSE catheters failed less often (6.6%) compared to traditional epidural catheters (11.6%). Within the first 30" of placement, more CSE catheter failures went undetected compared with traditional catheters (P=0.009). Overall, CSE has a lower risk of failure than traditional epidural catheters.

Dural puncture epidural (DPE) technique was first described nearly a decade ago and demonstrated improved maternal satisfaction and sacral analgesia by puncturing the dura without injection medication into the CSF. More recently, 124 parturients were randomized to CSE vs. DPE vs. CLE. Onset of analgesia was quicker in patients receiving CSE (2min) vs. DPE (11min) vs. CLE (18min). Top-ups were required less often and side-effects (pruritis, hypotension, asymmetric block) were less in the DPE group. The authors concluded that DPE improved the quality of analgesia with fewer side effects compared with CSE and CLE.

Programmed intermittent epidural bolus (PIEB) technique is used to deliver a mandatory bolus of local anesthetic solution by a programmed infusion pump to maintain analgesia rather than by a continuous infusion. However, optimal dosing regimens have not been established. Overall, studies have demonstrated decreased local anesthetic consumption, improved maternal satisfaction scores, reduced risk of motor blockade, decreased duration of the second stage of labor and decreased number of clinician rescue boluses in PIEB groups compared to continuous infusion groups.[28]

Nitrous oxide is an anesthetic gas with a rapid onset that is used as a labor analgesic around the world. Although its use was limited in the U.S. in 2012, its availability has been increasing. A recent chart review of nitrous oxide utilization at a large teaching hospital determined that 146 (3% of total deliveries) women chose nitrous oxide for labor analgesia.[29] The conversion rate to neuraxial analgesia was 63% compared to 85% in women who did not chose nitrous oxide. Labor induction and augmentation were associated with higher rates of conversion to neuraxial analgesia. Richardson et al.[30] evaluated maternal satisfaction as measured by a postpartum standardized survey. Data were available for 6242 (96%) women with 81% choosing neuraxial analgesia and 19% who chose nitrous oxide. More than 90% of women who received neuraxial analgesia reported high effectiveness. Women who received only nitrous reported variable analgesic effectiveness with ~50% reporting high effectiveness. The authors concluded that women who received only nitrous were "as likely to express satisfaction with anesthesia care" compared with women who received neuraxial analgesia, "even though they were less likely to report excellent analgesia." This study suggests that analgesia is not the only contributor to maternal satisfaction.

Remifentanil has been studied for the last two decades as an alternative to other parenteral opioids because of its rapid onset, short half-life, and potency. Although it is more often administered by a patient-controlled intravenous route for labor analgesia, a recent survey revealed ~36% of U.S. academic centers used remifentanil.[31] There were 14 serious maternal and neonatal complications (e.g., desaturation, hypoventilation,

and apnea). In addition, a recent review of remifentanil administration for labor analgesia outlines several concerns including its status as a Category C drug and manufacturers' concern, "the safety of remifentanil during labor or delivery has not been demonstrated" and "the drug should be given to a pregnant woman only if clearly needed benefit justifies the potential risk to the fetus."[32] Taken together, remifentanil may be considered when neuraxial labor analgesia is contraindicated. However, protocols and adequacy of monitoring are necessary to ensure maternal and neonatal safety.

Clinical Management of Critical Illness

Post-partum hemorrhage remains a significant cause of mortality and ICU admission. With childbirth, fibrinolysis occurs. Within 1 hour of birth, tissue damage from childbirth increases the concentration of tissue plasminogen activator. Tranexamic acid reduces bleeding by inhibiting the breakdown of fibrinogen and fibrin by plasmin. The role of tranexamic acid for postpartum hemorrhage was investigated by the WOMAN trial. In this large study, 20,060 women were enrolled to receive either tranexamic acid 1 gm (100 mg/mL) administered at a rate of 1 mL per min or placebo, when diagnosed with postpartum hemorrhage.[33] The most important finding of the study was that death due to bleeding was significantly reduced in women given tranexamic acid, especially if the treatment was initiated within 3 hours of delivery. In this large series, the incidence of thromboembolic events did not differ. Given these results, tranexamic acid should be considered when a parturient is diagnosed with postpartum hemorrhage.

Maternal Early Warning Systems are used increasingly to alert care providers of severe vital sign abnormalities that often precede clinical recognition of critical illness. Major maternal morbidity and mortality may be preventable. Recently, a study evaluated whether implementation of a maternal early warning trigger tool reduced maternal morbidity.[34] Clinical management pathways were introduced at 6 hospitals for early assessment and treatment of patients suspected of clinical deterioration in 4 of the most common areas of maternal morbidity: sepsis, cardiopulmonary dysfunction, preeclampsia-hypertension, and hemorrhage. Positive triggers were defined as "severe (single abnormal value): maternal heart rate (HR) >130 beats/min (bpm), respiratory rate >30/min, mean arterial pressure <55 mm Hg, oxygen saturation <90%, or nurse concern; or non-severe (required 2 abnormal values): temperature >38 or <36°C, blood pressure >160/110 or <85/45 mm Hg, HR >110 or <50 bpm, respiratory rate >24 or <10/min, oxygen saturation <93%, fetal HR >160 bpm, altered mental status, or disproportionate pain." Compared to non-pilot site hospitals, there were significant reductions in composite morbidity measures that were associated with the implementation of the tool, suggesting that widespread use of the tool may be useful.

Triggers, bundles, protocols, and checklists are also being used to improve obstetric care by aiding in the timely diagnosis and treatment of complications (e.g., hemorrhage) that often occur unexpectedly in otherwise healthy patients.[35] These tools are: 1) evidence-based to enable measurable outcome in quality improvement; 2) used to improve timely diagnosis in order to reduce morbidity; 3) customizable for local use; and 4) promote interdisciplinary patient-centered care. The maternal early warning criteria are an example of a trigger and were initially proposed in the U.S. by the National Partnership for Maternal Safety.[36] A hypertension bundle has been proposed that: 1) focuses on the differential diagnosis of hypertensive disease in pregnancy; 2) outlines criteria prompting evaluation and treatment; and 3) provides algorithms for administration of antihypertensives, checklists for managing eclampsia, and educational materials for quality improvement.[10] Another example relevant to anesthesiology is implementation of a postpartum hemorrhage protocol that escalates care and recommends early blood product transfusion.[37]

Cardiac arrest during pregnancy is exceptionally rare with an estimated incidence of 1:12,000 deliveries in the United States. The most common causes of arrest are hemorrhage, cardiovascular disease, sepsis, amniotic fluid embolism, pulmonary embolism, and sepsis. Current ACLS guidelines recommend that the guidelines for cardiopulmonary resuscitation be followed. During cardiac compressions, the patient should be supine with manual left uterine displacement. Perimortem cesarean delivery should be considered if there has not been a return of maternal circulation by four minutes.[38] The United Kingdom reported their experience with maternal cardiac arrest. From 2011 to 2014, there were 66 cases of maternal cardiac arrest resulting in an incidence of 2.78 per 100,000 deliveries. Of these 66 cases, 16 arrested solely as a consequence of obstetric anesthesia (12 of whom

were obese). Perimortem cesarean delivery was performed in 49 women resulting in a maternal survival rate of 58% and an infant survival rate of 66%.[39]

Maternal morbidity and mortality.

Rates of maternal mortality have decreased worldwide. However, the U.S. is an outlier in that rates of maternal mortality have increased despite the U.S. having "some of the most cutting edge medical treatments." Increased rates of cesarean delivery, advanced maternal age, co-morbid conditions, and diverse populations have increased the risk for adverse pregnancy events. Recently, documentation of maternal death has improved since death certificates now include a check-box indicating whether the death was pregnancy-related. Excluding California and Texas, the maternal mortality rate (per 100,000 live births) for the other 48 states increased 26.6% from 18.8 in 2000 to 23.8 in 2014.[40] Although rates of maternal death in Texas increased substantially during 2011-12, rates of maternal death declined in California, most likely related to the Maternal Quality Care Collaborative and implementation of bundles for hypertension, hemorrhage, and embolism. With greater focus by states on state-specific mortality data, a review of maternal deaths in Colorado (n=221) from 2004 to 2012 revealed that maternal suicide was the number one cause of maternal death in the state.[41] Thirty percent of the deaths resulted from self-harm (accidental overdose or suicide). Only 6 maternal deaths occurred during pregnancy. More than 50% of the cases had documented psychiatric diagnoses and 17% had a substance use disorder. Less than 50% of the patients went to a postpartum visit.

Racial disparities and their contribution to maternal morbidity and mortality have been an area of focus. Closer examination of interstate differences in rates of maternal mortality determined that racial disparities and social factors were important drivers of state differences in maternal mortality.[42] Study results suggested that there was a correlation between states and the proportion of deliveries to non-Hispanic Black women and the states' maternal mortality. Rates of unintended pregnancy, 4 or fewer prenatal visits, cesarean delivery, and unmarried mothers were also contributors. When 2010-11 data from the Nationwide Inpatient Sample were examined for whether "racial differences in the site of delivery contributed to black-white disparities in severe maternal morbidity", severe maternal morbidity was higher in hospitals with high black populations compared to low or medium black-serving hospitals.[43] Because site of delivery may be an important contributor to maternal morbidity. quality improvement efforts should be explored in these hospitals.

Complications related to neuraxial anesthesia.

Subdural hematoma associated with labor epidural analgesia. Lim, et al. [44] reported a series of subdural hematomas associated with labor epidural analgesia. In these eleven obstetric patients, six had some form of dural puncture while five patients did not. While it is difficult to conclude whether dural puncture, either intentional or accidental, is associated with subdural hematoma, there are other learning points. The majority of patients had the onset of headache approximately 4 days after performance of the anesthetic, suggesting that this diagnosis should be considered for a late onset headache. The authors were able to calculate an observed rate of subdural hematoma associated with epidural placement (1:3900) which increased to 1.1% (1 in 87) if a recognized dural puncture occurs.

Neurological deficits in the lower extremity are usually minor and transient with a predominant sensory component involving lumbosacral nerve roots or sacral cutaneous nerves following delivery. Recently, a prospective study evaluating postpartum obstetric neuropathies quantified and described these neurologic deficits.[45] Within 8 to 32h after delivery, 1019 of 1147 eligible women were evaluated for lower extremity numbness and/or weakness. Symptoms were reported by 3.4% and of those, 2% had documented neurological deficits. In these patients, lumbosacral plexopathies and cluneal nerve compressions were the most common. Parity, body weight, duration of labor, mode of delivery, or neuraxial block were not predictive of risk. However, a history of a neurological condition (OR 7.98) or back injury (OR 4.82) increased the odds of a deficit. Compared to the study by Wong et al.[46] who reported a median duration of deficits of 2 months, the patients in this study experienced symptoms lasting days and at the most several weeks, suggesting an injury of less severity.

Continuous spinal catheters are placed after inadvertent dural puncture or in high-risk obstetric patients. However, there are concerns for infection, nerve damage and post-dural puncture headache. A retrospective review of complications from 761 intrathecal catheters over a 12-year period, revealed failure rates of 3% when catheters were placed intentionally and 6% when the catheter was placed after accidental dural puncture. There were no serious complications (e.g., meningitis, epidural or spinal abscess, hematoma, arachnoiditis, cauda equine syndrome). The rate of PDPH was ~40% and epidural blood patch was 31%. The authors suggest that intrathecal catheters are a dependable option for labor analgesia and cesarean delivery.

Neuraxial hematoma and abscess are rare complications. In a study evaluating risk factors and incidence of neuraxial hematoma and abscess, 3.7 million neuraxial procedures were documented in the Nationwide Inpatient Sample from 1998-2010.[47] The incidence of spinal hematoma in obstetric patients was 0.6 per 100,000 epidural catheterizations (95% CI, 0.3 to 1.0 x 10^{-5}). The incidence of epidural abscess was zero in these patients. However, in non-obstetric patients, the incidence of spinal hematoma was 18.5 per 100,000 (95% CI, 16.3 to 20.9 x 10^{-5}). Risk factors for spinal hematoma included the type of surgery (e.g., vascular), hospital status, and patient comorbidity score. Results suggest that rates of these complications are low, especially in obstetric patients.

Postpartum Management

Neuraxial opioids should be considered for postoperative pain control following cesarean delivery rather than intermittent injections of parenteral opioids.[24] A recent meta-analysis studies determined whether low or high-dose morphine provided adequate analgesia in terms of duration and intensity with fewer side effects.[48] Higher-dose morphine was defined as >100-250mcg and lower-dose morphine was defined as 50-100mcg. Eleven articles met criteria with 233 patients in the higher-dose group and 247 patients in the lower-dose group. The time to first request for analgesia was longer in the higher-dose group. Morphine consumption at 24h and pain scores at 12h were not significantly different between groups. Incidence of other side effects including nausea/vomiting and pruritis were decreased in the lower-dose group. The authors suggest that clinicians should weigh risks and benefits of administering high-doses of intrathecal morphine for post-operative pain control.

Breastfeeding is the goal for all new mothers. Any factor that increases the difficulty of breastfeeding is more likely to cause new mothers to abandon it. The use of intrathecal morphine in addition to the local anesthetic was examined as to its effect on the neonate's ability to breastfeed.[49] As compared to intravenous morphine, there was no difference in the incidence of breastfeeding. The effect of epidural analgesia on the infant's ability to breastfeed was assessed. In a systematic review, 23 studies were identified.[50] To no surprise, the results were conflicting. Of the studies, 12 showed negative associations between epidural analgesia and breastfeeding success, 10 studies showed do effect, and only 1 study showed a positive association. Of these studies, only 3 were randomized. The major conclusion from the study is that the type of analgesia, duration of analgesia, confounds the literature examining breastfeeding and epidural analgesia methods of assessing breastfeeding, and failures to consider the mothers' intention to breastfeed. Parturients with diabetes, with substance abuse issues, or with preterm labor are less likely to breastfeed.[51]

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ANESTHESIOLOGY 2017
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Respiratory Physiology for the Anesthesiologist: Gas Exchange

Luca M. Bigatello, MD **Boston, Massachusets**

Respiration provides oxygen (O_2) and removes carbon dioxide (CO_2) for the body. A remarkable arrangement of functional units (the alveoli) delimited by extra-thin walls (epithelium and endothelium) creates the interface for gas exchange between air and blood. Gas- flow in and out of the lungs (ventilation) is generated by the activity of the respiratory muscles, or of a ventilator, and opposed by resistance within the airways and elastance ("stiffness") of lungs and chest wall. Knowledge of the basic physiologic events that regulate gas exchange provides a most useful frame to correctly interpret the information from your physiologic monitors during anesthesia, and properly set your anesthesia machine ventilator. Experience from the care of respiratory insufficiency in the intensive care unit ICU also supplements the anesthesiologists' armamentarium in the most complex cases such as multiple trauma, thoracic anesthesia, and laparoscopic head- down position cases.

The PaO_2.

How O_2 gets from the atmosphere to the arterial blood: the alveolar air equation. O_2 constitutes 21% of the air we breathe. At sea level, air exerts a pressure of 760 mmHg; once fully saturated by water vapor (47 mmHg), the PO_2 in the inspired air (PiO_2) can be calculated as:

$$\mathbf{PiO_2} = (760 - 47)\ \text{mmHg} \times 0.21 \approx \mathbf{150\ mmHg} \qquad [1]$$

In the alveoli, one volume of O_2 is exchanged for 1.2 volumes of CO_2 (respiratory quotient [RQ] of 0.8): with a normal $PaCO_2$ of 40 mmHg, the alveolar PO_2 (PAO_2) at steady state will be:

$$\mathbf{PAO_2} = PiO_2 - PaCO_2 \times 1.2 \approx \mathbf{102\ mmHg} \qquad [2]$$

Past the pulmonary capillaries, arterial blood normally receives a small fraction of venous blood from a minimal alveolar shunt (2 - 3%, increases with aging) and from blood that shunts the pulmonary circulation, such as the bronchial veins and some diaphragmatic veins, and PaO_2 decreases slightly below 102 mmHg.

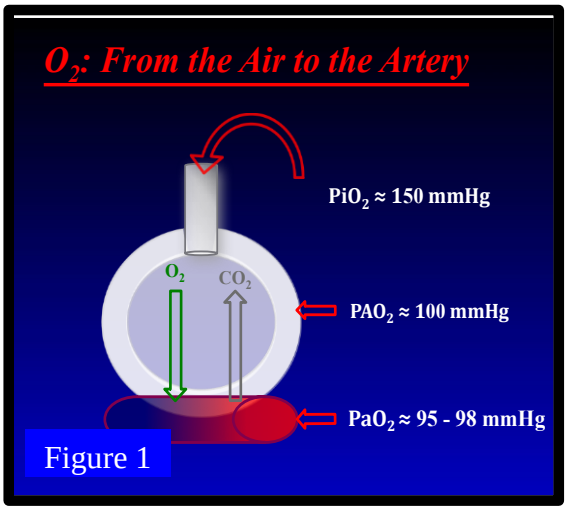


Figure 1

Causes of hypoxemia. Understanding how O_2 moves from the air to the blood (**Figure 1**) provides a convenient framework to classify the various causes of hypoxemia:

Low PiO_2. The most common cause of a low PiO_2 is breathing at high altitude. Breathing air at 5,300 feet in Denver lowers PiO_2 to 120 mmHg, and breathing air at 30,000 feet on the summit of Mount Everest lowers the PiO_2 to 40 mmHg (which is equal to the normal *venous* PO_2! see Figure 2). Although rare, causes of low PiO_2 at sea level are related to the accidental administration of a hypoxic mixture.

Low PAO_2. Hypoventilation: in addition to hypercapnea, hypoventilation may cause hypoxemia by increasing the alveolar PCO_2 ($PACO_2$). A $PaCO_2$ of 80 mmHg will decrease PAO_2 to 150 - 80 x 1.2 = 54 mm Hg. This scenario underlies the importance to immediately administer supplemental O_2 to a patient that appears to be hypoventilating (for example, in the PACU): supplemental O_2 will rapidly increase PiO_2 and PAO_2 offsetting the effects of a high $PACO_2$.

Impaired diffusion across the alveolo-capillary membrane rarely is direct cause of hypoxemia. In situation like alveolar edema, where fluid increases the distance between alveolar air and the capillary, diffusibility of O_2 is such that PaO_2 would be only minimally affected; contrary to frequent say, the hypoxemia of pulmonary edema is due primarily to ventilation / perfusion (V/Q) mismatch rather than impaired diffusion. The diffusing capacity of carbon monoxide (DLCO) is a sensitive test to quantify impairment of lung function, although primarily as a consequence of abnormality in V/Q rather than of gas diffusion *per se*.

Low PaO_2. The most common cause of hypoxemia is intrinsic lung disease, which alters the matching of ventilation and perfusion. **V/Q mismatch** defines a continuum that ranges from no ventilation with preserved perfusion (**shunt**), to no perfusion with preserved ventilation (**dead space**) including an infinite number of combinations.

Shunt results in venous blood (PvO_2 = 40 mmHg, **Figure 2**) reaching the arterial side without addition of O_2, thus decreasing PaO_2 to a degree depending on the size of the shunt. The fraction of total pulmonary blood flow (Qt) shunted away (Qs) from unventilated alveoli can be calculated as the difference in content of O_2 between the pulmonary capillary (CcO_2) and the arterial (CaO_2) and venous (CvO_2) blood:

$$\mathbf{Qs/\ Qt} = (CcO_2 - CaO_2) / (CcO_2 - CvO_2) \quad [3]$$

where CcO_2 is calculated using PAO_2 as a surrogate of PcO_2. Content of O_2 is:

$$\mathbf{Content\ O_2} = Hb \times 1.34 \times O_2\ Sat. + PaO_2 \times 0.003 \quad [4]$$

Shunt occurs with intracardiac defects and in diverse pulmonary pathology such as atelectasis, pneumonia, and the acute respiratory distress syndrome (ARDS). In the presence of shunt, increasing FiO_2 will only marginally improve PaO_2 (through an increase in PvO_2); only recruitment of collapsed alveoli will effectively treat the hypoxemia.

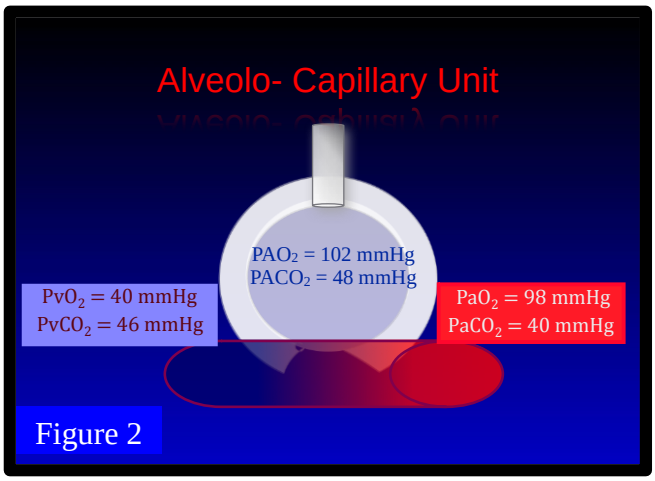


Figure 2

Low $\dot{V}/\dot{Q}$ results in arterial gas tensions approaching those of venous gas (Figure 2). Despite multiple possible combinations of low and high V/Q often present at the same time, **hypoxemia** is predictably the main result, because low V/Q and high V/Q do not cancel each other out. This is due to the shape of the **O_2 dissociation curve**. In a low V/Q alveolus where PaO_2 approximates PvO_2, *e.g.* 50 mmHg, O_2 Sat. will be ~ 75%, which will decrease CaO_2 by 25%; in an alveolus with a correspondently high V/Q ratio, O_2 Sat. cannot rise beyond the normal 100%, hence cannot compensate for the lost 25%; an increase in PaO_2 even well beyond 100 mmHg will compensate minimally because only 0.003 of the new PaO_2 will contribute to the CaO_2. **Figure 3** exemplifies this concept: the O_2 content leaving the alveolus with a low V/Q (16 mls / 100 mls of blood) approximates that of venous blood (14 ml) but the O_2 content leaving the alveolus with a high V/Q (20 mls) is barely higher than that of the normal alveolus (19 mls).

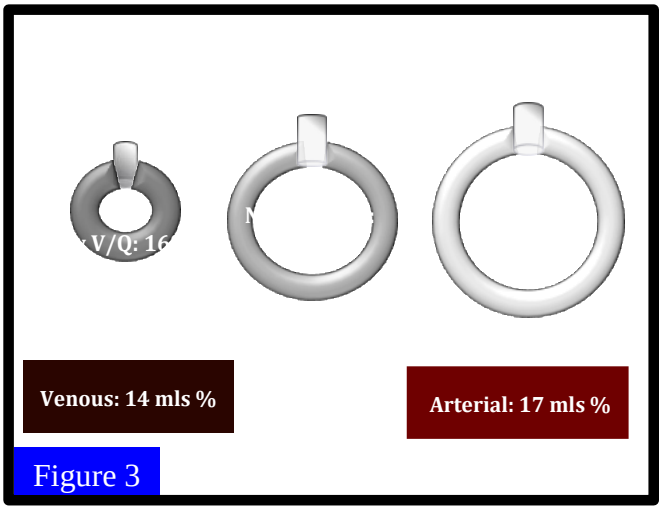


Figure 3

Low PvO_2 feeds venous blood into the arterial circulation through areas of shunt. The extent of the resulting hypoxemia depends on the magnitude of the shunt, and is limited by local hypoxic vasoconstriction (HPV) that reduces blood flow through the shunted areas. Through this mechanism, a low PvO_2 may cause significant hypoxemia in two clinically relevant circumstances. *First*, during shivering, due to an increase in O_2 consumption; *second*, with a low cardiac output, due to increased O_2 uptake (that's how hypotension may cause hypoxemia!).

Hypoxemia kills. Treatment of hypoxemia must be swift, and luckily it is simple during the administration of anesthesia in an uncomplicated case, i.e.: just increase the FiO_2! Not the same in the ICU during respiratory failure or in the OR in patients with severe respiratory comorbidity or during particularly procedures such as one- lung ventilation, thoracic trauma, pulmonary hemorrhage, etc. Hypoxemia kills by depriving cells of their main fuel: when PaO_2 decreases significantly, the gradient that drives O_2 from the blood into the interstitium ($PO_2 \approx 20 - 30$

mmHg) and from the interstitium into the cell (PO_2 < 20 mmHg) decreases as well. It is important to note that this is PO_2, not O_2 content (Equation [4]) hence therapy is strictly on PO_2, not on the other elements of O_2 content.

The $PaCO_2$.

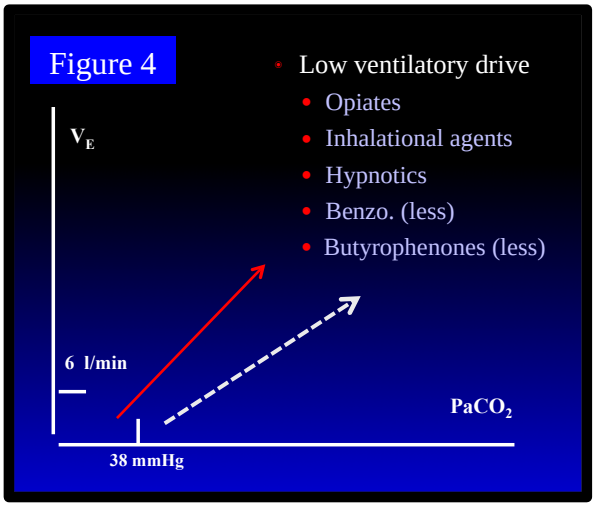
CO_2 and H_2O are end products of aerobic metabolism. CO_2 is transported in blood as carbammino compounds, bicarbonate, and dissolved. The latter determines the $PaCO_2$, and is eliminated as gas from the lungs. At steady state, $PaCO_2$ results from the equilibrium of production ($\dot{V}CO_2$) by cellular metabolism and elimination by the minute ventilation (V_E):

$$\mathbf{PaCO_2} = \dot{V}CO_2 / V_E \qquad [5]$$

$PaCO_2$ is a potent stimulant of ventilation: for each increase of 1mmHg $PaCO_2$, the V_E increases nearly instantly by 1 - 2 l/min. An alteration in this relationship is a common cause of hypercarbia (**Figure 4**)

Causes of hypercarbia.

High $\dot{V}CO_2$ occurs with fever, shivering, excessive caloric / carbohydrate intake, and, to its maximum extent, in malignant hyperthermia (MH) and neuroleptic malignant syndrome (NMS). Except for MH and NMS, the increase of $\dot{V}CO_2$ is generally transient, and may be offset by an increase of V_E.



Low CO_2 elimination is the most common cause of hypercarbia and it includes two main reasons:

Hypoventilation increases $PaCO_2$ by limiting CO_2 elimination. Common causes of hypoventilation include: *a)* a decreased central drive to breathe, as it occurs with the administration of hypnotics and opiates (**Figure 4**); *b)* respiratory muscle weakness, in syndromes such as Guillain-Barre' and polyneuropathy of critical illness; and *c)* high resistive or elastic ventilatory loads (below), as it occurs in severe asthma or abdominal distention. Immediate treatment of hypoventilation includes ventilatory support and supplemental O_2 (see *hypoxemia*).

Dead space and high V/Q are a continuum of the same phenomenon, similarly to what we discussed for shunt and low V/Q. As perfusion decreases, venous blood fails to reach the alveolus, and less CO_2 is eliminated; exhaled PCO_2 decreases and, at a constant $\dot{V}CO_2$, $PaCO_2$ rises. These phenomena are at the basis of the measurement of the physiological dead space, as the fraction of unperfused ventilatory space ("dead", V_D) over the tidal volume (V_T):

$$\mathbf{V_D/V_T\ phys} = (PaCO_2 - PECO_2) / PaCO_2 \qquad [6]$$

V_D/V_T phys includes anatomical (proximal airways) and alveolar dead space (V_D/V_T alv). V_D/V_T phys is calculated using mean exhaled PCO_2 ($PECO_2$), which is measured as the PCO_2 averaged over several breaths. While the anatomical dead space is for the most part fixed (25- 30% of V_E) V_D/V_T alv is 0 in normal lungs, and it increases with the degree of lung disease in a number of conditions, such as ARDS and COPD / asthma. V_D/V_T alv can be calculated as:

$$\mathbf{V_D/V_T\ alv} = (PaCO_2 - PetCO_2) / PaCO_2 \qquad [7]$$

$PetCO_2$ is the PCO_2 at end- expiration- 'end-tidal'. In a standard capnogram, when the expired CO_2 reaches a plateau, the $PetCO_2$ is highly representative of the $PACO_2$. A normal $PECO_2$ is approximately 30 mmHg, and a normal $PetCO_2$ is 38 - 40 mmHg, nearly the same as $PaCO_2$.

The linear correlation between $PaCO_2$ (independent variable) and V_E (dependent variable) gives us a clinical tool to follow changes on a ventilator without the need to measure $PaCO_2$ at each change in settings, similarly to how we may follow O_2- Sat. without measuring PaO_2. If we take note of the V_E before implementing a change, and we know the $PaCO_2$ at that V_E, no significant changes in V_E will reassure us that no significant change in $PaCO_2$

occurred. That is, with some caveats: *a)* assuming the $\dot{V}CO_2$ has not changed; unless we have a volumetric capnograph in use (unusual) we rely on our judgment: fever, shivering, and agitation may increase $\dot{V}CO_2$, which we need to verify; and *b)* assuming the V_D/V_T has not changed; this can be verified following the $PetCO_2$ from a time-based capnograph, used routinely in the OR and frequently in the ICU.

Hypercarbia rarely kills. Differently from hypoxemia, which must be corrected promptly, hypercarbia per se is generally well tolerated unless severe enough to cause obtundation leading to respiratory arrest, mostly at $PaCO_2$ levels above 100 mmHg. However hypercarbia may cause severe morbidity through various mechanisms in susceptible patients, such as by increasing intracranial pressure in the presence of cerebral edema, or exacerbating pulmonary hypertension in children with congenital heart disease and in adults with pre-existing right ventricular dysfunction. On the other hand, moderate hypercarbia could be a favorable condition in a number of pathologic situations, such as in shock by improving local blood flow, and in ARDS by allowing to limit tidal volume below levels known to be injurious.

Clinical applications of gas exchange physiology.

Anesthesia and Hypoxemia.

A number of factors conjure to decrease PaO_2 during general anesthesia.

Decreased lung volumes. A decrease in functional residual capacity (FRC) occurs within minutes of induction of anesthesia, with or without neuromuscular blockade, and is exacerbated by associated factors that also reduce FRC, such as morbid obesity, pregnancy, and acute respiratory failure of the low compliance type, for example ARDS. Oxygen desaturation may occur early and hastily following induction, getting the tonality of your pulse oximetry down to a baritone awfully fast if you cannot intubate swiftly. Under ideal circumstances, a calculation based on the volume of O_2 in the FRC and the average O_2 consumption shows that as much as 8 minutes are available prior to severe hypoxemia to occur. However, the clinical situations mentioned above drastically reduce this time frame; planning in advance is key in these circumstances to best utilize the short time available. A decrease in lung volumes, both FRC and tidal volume, may continue through during maintenance of anesthesia if ventilation is unsupported or only minimally supported, like for example with a low Pressure Support Ventilation (PSV) level. Getting the patient to breathe spontaneously may be helpful for other reasons, but supporting ventilation with positive end expiratory pressure (see below) a degree of inspiratory pressure to generate an adequate tidal volume is key to optimize gas exchange

Atelectases develop during anesthesia as a consequence of decreased lung volumes and / or of a high inspiratory fraction of oxygen (FiO_2). A high FiO_2 reduce the concentration of nitrogen in the alveoli, which otherwise contributes to maintain the alveoli open at end expiration because nitrogen is not part of the exchange of gases. Thus the name of *absorption atelectasis*, and the benefit of avoiding excessively high FiO_2 unless needed to treat severe hypoxemia. It has been calculated that the presence of just 20% nitrogen may limit the degree of alveolar collapse due to high FiO_2.

Oxygen toxicity in the perioperative period. High FiO_2 can produce local and systemic damage through the generation of reactive oxygen species (ROS), which trigger chain reactions of lipid peroxidation that damage nuclear and cellular membranes and denature DNA. The clinical significance of the potential actions of ROS is still vague, and just a few data are well established: *a)* local damage resulting in a decrease in vital capacity (VC) may occur after 24 hours of breatihing 100% FiO_2; further exposure may result in widespread lung injury; *b)* in one-lung ventilation, the combination of 100% FiO_2 and barotrauma may be additive in the pathogenesis of perioperative lung injury; *c)* data on the benefit of high FiO_2 ($\geq$ 80%) in preventing surgical site infection and nausea and vomiting have not been consistently produced; *d)* high FiO_2 in neonates is clearly associated with the development of severe ocular, cerebral, and respiratory toxicity; *e)* high FiO_2 in the elderly may also be associated with lung and systemic toxicity, but the clinical evidence is still frail.

Lung ventilation and alveolar recruitment during anesthesia.

Positive end- expiratory pressure (PEEP). The decrease in lung volumes that occurs during general anesthesia leads to a variable degree of alveolar *derecruitment* and hypoventilation. The most common way to prevent hypoxemia is

to add PEEP to your ventilator settings. PEEP prevents alveolar units to fully collapse on expiration, thus improving V/Q match (see earlier in the outline) and rising PaO_2; also, by opening alveoli that were previously collapsed, lung volume increases for the same inspiratory airway pressure, which is to say that *lung compliance* improves (see below for more on compliance). Going into a bit more depth, PEEP works through an increase in *mean airway pressure*, (MAP) which is the pressure in the alveoli (measured at the airway) throughout the duration of inspiration.

MAP = inspiratory pressure – PEEP x Tinsp./Ttotal +PEEP [6]

Hence, MAP increases by rising inspiratory pressure (and tidal volume), inspiratory time (Tinsp), and PEEP. Note that in many anesthesia ventilators you will not find a knob for "inspiratory time": most commonly you adjust the time through changes in I:E ratio; also note that when on volume control a change in Tinsp leads to an opposite change in inspiratory flow and inspiratory pressure, because now the ventilator has to deliver the same tidal volume in a shorter time.

Separating peak and plateau pressures. As the flow of gas enters the lungs, it generates a pressure in the airways, then in the alveoli, and then changes lung volume (tidal volume). Thus, the pressure that we measure at the airway during inspiration is the results of a number of factors: the inspiratory flow, the tidal volume, the resistance generated by the airway, and the compliance of lung and chest wall ($\mathbf{C_{L+CW}}$). The pressure at end inspiration, or peak inspiratory pressure (PiP) is often quoted as the pressure that recruits or damages the lung, but this is incorrect. The portion of PiP due to airway resistance (**Raw**) dissipates along the airways before reaching the alveoli. An effective way to understand this concept occurs if you briefly kink the endotracheal tube with your fingers. The PiP will sky rocket, but the tidal volume will not increase (in fact, will decrease) and the lung will not be damaged. Hence, in the presence of an elevated Raw, PiP does not correctly reflect alveolar pressure. The latter can be estimated by performing an *inspiratory hold* maneuver (**Figure 5**), which interrupts gas flow separating the resistive and elastic components of the PiP. Once inspiration is held, the pressure (Pip) drops to a lower level (plateau pressure [Pplat]) that is determined only by the size of the tidal volume and the $\mathbf{C_{L+CW}}$. Accordingly (**Figure 5**):

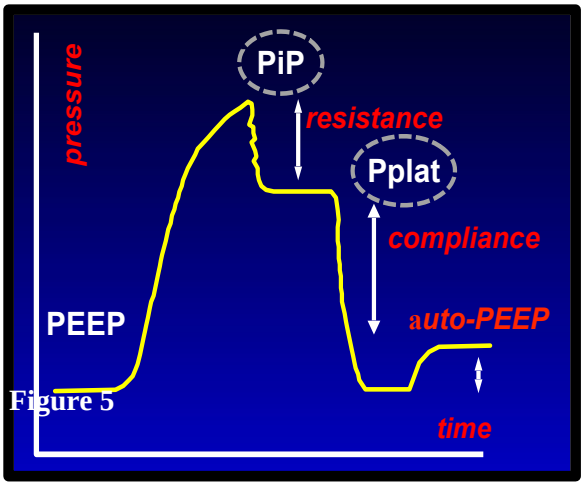


Figure 5

$\mathbf{C_{L+CW}}$ = tidal volume / (P_{PLAT} - PEEP) [9]

Raw = (PiP - P_{PLAT}) / $\dot{V}$ [10]

Under normal circumstances, the separation between PiP and Pplat is minimal, and it widens in the presence of asthma, COPD, and acute bronchospasm.

Lung collapse during laparoscopic / robotic surgery.

Lung, chest wall, and transpulmonary pressure (Ptp). Abdominal insufflation during laparoscopic surgery further decreases FRC; addition of a steep head- down position during, for example, GYN procedures compound the loss of lung volumes, and may require very high airway inspiratory pressures to achieve adequate ventilation. This situation has rattled the mind of anesthesiologists who are concerned about lung damage from the high pressure, to the point of sometimes asking to abort the surgery. However, a more thoughtful assessment of the mechanics of ventilation in the presence of elevated intra-abdominal pressure will somewhat reassure the apprehensive anesthesiologist. The concept that needs to be considered is that of *transpulmonary pressure (Ptp)*, or pressure across the alveoli, which is the true pressure that expands or that damages the lung:

Ptp = Palv – Ppl [11]

Where Ppl is the pressure in the pleural cavity. In a situation of low compliance of the lung (C_L) such as in ARDS, most of the inspiratory pressure is dissipated against the alveoli and little goes across into the pleural space, resulting in high Ptp. In the situation of low compliance of the chest wall (C_{CW}) such as with abdominal insufflation, little pressure is dissipated against the alveoli, and it moves into the pleural space where it dissipates against the stiff chest

wall, and Ptp is relatively low. Hence, for the same Pplat, we may have a high (ARDS) or low (laparoscopic surgery) Ptp. The first case represents a high risk for alveolar damage, the second does not.

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Ambulatory surgery post-discharge problems: What are they and how should we deal with them?

Johan Raeder, MD, PhD **Oslo, Norway**

Introduction:
The concept of ambulatory surgery implies that we only see the patient peri-operatively, including a very short period after their surgery. This is in perspective with days and even weeks to come before the patient is fully recovered in all aspects. Incorrectly we often assume as long as there is no re-admission or no spontaneous complaints, everything is fine. Still, there are quite some problems which may be evident after discharge, although these are not studied as extensively as all the aspects during the patient´s stay in the clinic or hospital. Actually, data may suggest that some complaints, such as nausea or vomiting, are more frequent after discharge although they may not be as strong (1). A high frequency of problems may also have to do with patients not having access to the same options and remedies for prophylaxis and treatment after discharge. Also, expectations may play a role; some think that once they are out of hospital, everything should be normal. This may include resumption of more vigorous activities which may provoke problems not evident while resting in the ward.
Patient information before discharge, and follow up later on, is a shared responsibility between the surgeon, the anesthesiologist, nurses and other staff members. Who is doing what, may vary from one institution to another, and also medico legal aspects are important in this context. Everyone should adopt their routines to what is practical and legal in their setting. Also the patient ´s responsibility should be clarified, instructions should be both written and verbal, and in most settings a confirming signature on everything understood and accepted is wise to obtain.
It is important to emphasize, both for patients and health care personnel, that some post-discharge problems are signs of potential serious complications, such as bleeding, infection or localized tissue ischemia, and should be discussed with professionals. All ambulatory surgical patients must have access, at all time, to a telephone service for rapid, adequate and friendly discussion and service regarding post-discharge problems.
Also, a good advice is to have a telephone call to ambulatory patients the day after surgery in order to ensure that side-effects are in control, and that instructions on medications and other measures are well understood and implemented.

Preparing the patient for the post-discharge period:
The basic and best preparation is, of course, to do a smooth and uneventful surgery and anesthesia, by minimizing the surgical trauma, the total drug load and the interference with normal homeostasis. The surgeon should appreciate the beneficial role, in most cases, of long-acting local anesthesia in the wounds, both in terms of analgesia and opioid sparing effect. The anesthesiologist should think about the recovery and post-discharge period from the very first drug given, and subsequently in terms of adequate prophylaxis of pain and nausea before discharge.
During the stay in the ambulatory unit a record on patient risk factors for pain and nausea should be made, in order to tailor the prophylactic drugs planned for post discharge effects.
Fulfilling the usual discharge criteria is by itself a step in ensuring a smooth course further on. Having an escort and a responsible person at home is an important safety issue, and will also add to quality by helping the patient in avoiding side-effects and support necessary measures to be taken. The ability to tolerate fluid is needed for tablet treatment at home. The criteria of no nausea and minimal pain, makes a promise for further smooth course. Still, it should be remembered that drugs given iv or as infiltration or blocks for optimized recovery and pre-discharge control, will wean out and not be effective anymore at some time after the patient comes home.

Pain:
The natural course of non-treated pain after a surgical trauma may be up to one week of resting pain, and 2-3 weeks or more, for pain during provocation or movement. It is still a controversial issue whether aggressive initial pain treatment may improve the prognosis of pain later on and reduce the risk of chronic pain (2). Still, while respecting the analgesic drug side-effects, the patient will benefit in perceived quality of initial aggressive pain prophylaxis (i.e. preventive analgesia) and treatment throughout the post-discharge period. It is generally harder to treat strong acute pain, than to prepare the patient by prophylactic analgesia in order to not have strong pain. A special problem, not

being extensively discussed or studied, is the strong breakthrough pain which may emerge when a successful long-acting local anesthesia block ends, typically late evening or during the first night (3). It seems like local anesthesia infiltration has a more smooth and gradual clinical offset, typically less rebound pain and even benefits in terms of less need of rescue analgesia after analgesia after the effect is ended(4).

Looking for special risk factors of more than average pain after a specific procedure, is a new concept which still is evolving. Such risk factors include: female gender, young age, ongoing preoperative pain of any kind (site of surgery or other site), pre-operative use of opioids, catastrophizing personality, anxiety or depression (5). Patients with a number of these risk factors present, should have special attention as to their analgesic prophylaxis being enforced. Also, pain during the stay in the post-operative care unit (PACU) will provide valuable input on what to expect after discharge.

During the stay in the ambulatory surgery unit the patients should have received proper multimodal non-opioid pain prophylaxis, which should be continued during the post discharge period. Basis should be regular, oral paracetamol (dose 0.5-1 g bid 4, according to age and weight) combined with NSAID. The rectal route is more unpredictable in terms of speed and bio-availability of drug, compared with the oral, and should only be used when oral administration is not feasible (i.e. children, some tonsillectomies, strong nausea/vomiting).

The choice of NSAID, traditional versus cox-II selective, and choice of drug within each group should be based on considerations of side-effects and practicalities; such as over-the counter availability, compliance as to bid one versus bid four, etc. It has not been shown that 1-2 weeks use of either NSAIDs or COX-II inhibitors pose any significant risk of increased cardiovascular morbidity or impaired healing, and the data for long-term use is still conflicting (6). As the patient should have hemostasis when leaving the unit, there is no major issue as to the minor increased risk of bleeding due to less thrombocyte adhesion with traditional cox-I selective NSAIDs. However, the side-effect profile with more gastrointestinal problems, allergy and asthma with cox-I inhibitors should be considered. Also the longer dose-interval of the cox-II selective drugs (bid 2 for celecoxib, bid 1 for etoricoxib) may be an advantage. As to renal problems, all NSAIDs may pose an increased risk, and for this reason care should be taken by prescribing NSAIDS to elderly, patients with known reduction in renal function and patients who use angiotensin-II blockers.

Glucocorticoids should not be repeated in the post-discharge phase, but the benefit on anti-emesis and analgesia will last for 1-2 days after administration of a single dose peri-operatively(7). No significant side-effects or contra-indications are shown for such use, but transient increased blood sugar in the diabetic should be addressed. The dose should be in the range of 8-16 mg iv dexamethasone for analgesia, whereas a dose of 4 mg may be sufficient for anti-emetic effect only. Whereas pregabalin and gabapentin both has shown minor, but consistent additive effect on postoperative pain (8), care should be taken in the ambulatory setting by starting these drugs post-operatively just before discharge as some patients may get hypotensive and faint at home. These drugs may be useful in special cases, then preferably starting as premedication, observing the effect in the PACU before discharge.

Local anesthesia adjunct should be a routine part of most ambulatory surgical procedures when feasible, either as dedicated infiltration of ropivacaine 2 mg/ml in the wound area or stronger solution as an appropriate nerve block, especially useful for surgery on the extremities. Bupivacaine may be an alternative, but pay attention to higher cardiovascular toxicity. Liposomal bupivacaine is an expensive and modestly effective adjunct (9). Although providing release of bupivacaine for 48-72 hours, the dose will be fairly low and not adequate for pain relief by itself.

For most ambulatory patients a repeated or continuous block by catheter may be impractical or unnecessary, although some reports of sending patient home with elastomeric local anesthesia pumps have been successful (10).

Whether a single shot block for surgery should be long lasting (i.e ropivacaine) or shortlasting (ie. lidocaine or mepivacaine) may be considered, depending upon whether rapid resumption of motor and sensory function is more or less of a benefit than prolonged pain relief for some extra hours. In some studies the addition of dexamethasone to local anesthesia solution has shown to prolong the analgesic effect further(11), in other have adding ketorolac proven more efficient topically than intravenous (12).

Rebound pain may be a severe problem after resolution of nerve blocks (see above), and should be prepared for by instructing the patient in taking paracetamol and NSAIDs well before the block is expected to wear out. A single dose of dexamethasone and long-lasting cox-II inhibitor (i.e. etoricoxib) peri-operatively may probably be a better measure, as these drugs acts on the wound inflammation and have effect until next morning or longer (Holmberg A, data on file).

The opioids have a long list of side-effects which are important after discharge: nausea, dizziness, constipation, disturbed sleep pattern and respiratory depression (13). For this reason the dose of opioids should be minimized by

optimizing the non-opioid options (see above) and further adjusted according to individual needs. Many moderate or extensive ambulatory surgery procedures may still be in need of "opioid-on-top" of an otherwise well designed non-opioid multimodal regimen. For oral post-discharge use, oxycodone is a good alternative for strong opioid effect, because it is predictably and readily absorbed by the oral route. A combined formulation of oxycodone and naloxone have been tested out successfully for less constipation with long-term use in cancer patients, but during a 3 day study period after gynecological surgery no benefit of this formulation was seen (14). Oxycodone, combined ordinary+ depot formulations, may be used, or rapidly absorbed tablets, according to need. The slightly weaker opioids, such as tramadol and tapentadol are better in terms of less constipation, less risk of addiction and other side-effects, they also have a combined effect on opioid and non-opioid spinal analgesic receptors. Tapentadol has less risk of nausea than tramadol (15) and may for this reason be preferred. Codeine is a pre-drug which is slowly metabolized to morphine. While extensively used for decades, the popularity is declining due to the fact that 5-10% of a western population do not convert the codeine to active drug, whereas a very small proportion have a very extensive conversion with danger of unexpected strong effect.

Post-discharge nausea and vomiting (PDNV):
Post-discharge nausea and vomiting is a very common problem, often not being addressed properly. By definition of discharge criteria, patients should have no nausea or vomiting at that time. Still, an incidence of 36-47% nausea or vomiting later on has been noted in a recent review (16). PDNV may by initiated by being mobilized during home transport and later at home, when taking oral opioids for pain relief and having disturbances in normal feeding and sleeping habits. A special feature with PDNV is that oral drug treatment may fail to come into systemic circulation, because drugs may be not reach the intestine, either due to vomiting or gastric paralyses. Non-pharmacological measures are frequently used by the patients (17), such as resting, fresh air, cold forehead dressing etc. Oral disintegrating drugs, mixtures, rapid soluble formulations or suppositories may be an option of formulation in a patient with ongoing PDNV (18). However, prophylactic measures are definitely to prefer and should be tailored to the patient´s individual risk. Risk factors of PDNV include: female gender, age less than 50 yrs., history of previous PONV or travel sickness, use of opioids in the PACU and occurrence of PONV before discharge (1). A score of 0 out of these items resulted in 7% incidence of PDNV, whereas a score of 5 items resulted in 89% incidence (1). Important perioperative prophylactic measures include regional anesthesia/analgesia techniques, propofol instead of inhalational anesthesia and minimizing the need of post-operative opioids with optimal multimodal non-opioid analgesia. Adding 5-HT3 blocker, glucocorticoid and neuroleptic drug (i.e. droperidol or haloperidol) may all provide additive prophylaxis until next morning for each drug added. For prophylaxis beyond 24 hrs the glucocorticoid may still be efficient, as well as a scopolamine patch on the skin. The latter may result in unpleasant side-effects such as dry mouth, blurred vision and confusion in the elderly, but may have a long lasting anti-emetic effect for many days. P6 acupressure or permanent acupressure with a band may also have a modest, but significant anti-emetic effect during days. More expensive options, such as long lasting 5-HT3 blocker (i.e.palonosetron) or NK1 antagonist (i.e. aprepitant) may have a duration of effect for up to 48 hours when given prophylactically (19). For treatment of PDNV, oral disintegrating ondansetron may be tried (18), and also tablets or suppositories of neuroleptic drugs or metoclopramide.
In order to prepare patients for home travel, especially in those cases where mobilization to sitting position provoke pallor or discomfort, a dose of ephedrine 5-10 mg iv supplemented with 30-40 mg subcutaneously may be a very good anti-emetic prophylaxis for the home travel and the subsequent 3-4 hours (20) .
An important aspect of serious or prolonged PDNV is to inform the patients about the dangers of getting into dehydration or electrolyte disturbances, in some cases calling for a re-admission and proper iv treatment by drugs and fluid.

Cognitive dysfunction:
Whereas delirium usually develops shortly after surgery and may result in un-planned admission, cognitive dysfunction is less evident and less dramatic in appearance and may go on for weeks and months after surgery. Delirium is a state of acute confusion, either agitated or silent, i.e. only evident when asking the patient about simple issues on orientation. Cognitive dysfunction is a decline in abilities to perform more complex cognitive tasks, such as doing a puzzle, crossword and reasoning about an issue (21). Established risk factors of cognitive dysfunction are major surgery, age, previous dementia, being an inpatient (22); whereas use of regional anesthesia versus general anesthesia is of more controversial impact (23). Post-operative cognitive dysfunction is a reversible state, within days or months patients get back to their normal baseline function, which however may be reduced from start by a

pre-dementia state. Patients and relatives should be aware of the transient nature of post-operative cognitive dysfunction, help the patient with tasks of demanding intellectual challenges, and provide a stable, predictable and secure environment for the patient.

Orthostatic hypotension, fainting:
These are poorly described and characterized conditions. Traditional fainting may be caused by dehydration or by pain or nausea via vasovagal reflexes, or by drug actions on blood-pressure(e.g. clonidine, pregabalin, gabapentin). The state of postoperative orthostatic intolerance is characterized by symptoms of dizziness, nausea, vomiting, blurred vision or syncope during sitting and standing during early mobilization. It is a transient condition, usually resolving within 24-48 hours. It is reported in between 12-60% of patients (24), more with extensive surgery than minor. Female gender is a risk factor, also use of opioids and regular anti-hypertensive medication. The pathophysiology seems to be attenuated endogenous vasopressor response when mobilizing and increased vagal output, potentially associated with inflammatory activation during surgery and tissue trauma(24).

Fatigue:
Postoperative fatigue is a frequent condition after surgery, not receiving much attention from research or health care personnel. Still, a high proportion of patients will have a state of physical and/or mental tiredness or weakness throughout the first days or even weeks after ambulatory surgery. They feel worn out and in low energy. The condition is poorly understood, but seems associated with extent of surgery, tissue damage and inflammation. In a recent study comparing desflurane with propofol for maintenance during ambulatory cholecystectomy, average fatigue was very similar between the two methods; peaking at day three after surgery and back to baseline at day seven(25).

Obstructive sleep apnea (OSAS) and sleep disorders:
Most patients will encounter sleep disturbances after discharge. The impact of opioids and residual anesthetic drugs may result in a low-quality sleep during the first night after the procedure. Increased day-time sleep may also occur, whereas later on there may be catch-up nights with increased fraction of REM sleep and dreams (26).
Patients with obstructive sleep apnea syndrome should preoperatively be carefully screened for safe same day discharge, with a low threshold for admission to hospital when in risk for severe obstruction (27). After discharge they should be advised to use CPAP for the first days at least, and to be careful with opioids.

Surgical issues:
Wound care: Ambulatory surgical wounds are usually closed with absorbable sutures or glue and covered with a dry dressing. The usual advice is to keep the dressing on and dry for 1-2 days, then change to a smaller plaster. Gentle shower, preferably avoiding soaking the wound dressing, may be allowed during first evening, but better to wait until next day. If the dressing gets wet, then it should be changed, also if blood or tissue fluids soak through the wound dressing. A little blood or oozing the first 1-2 days may be normal, but if abundant or increasing, health care professionals should be contacted for advice or inspection. After 3-4 days, most minor wounds may not need coverage, and normal washing and showering may be allowed, although full immersion into bathtubs or pools may be postponed for some further days.
In the rare cases of wound drains (i.e. some plastic surgery) in ambulatory patients, strict hygiene is important in handling, until drains are removed by professionals after 1-2 days.
Bleeding: Generally there should be hemostasis in the wound area and surgical site at discharge. Thus, any bleeding in the post-discharge period should be discussed immediately with a health care professional. Exceptions are minor oozing from an otherwise normal wound and limited amounts of coagulated or old blood in secretions from body openings being subjected to procedural manipulation or surgery. However, special attention should be paid to non-visible bleeding or development of hematomas. Patients should be instructed to look for such, specific signs according to type of procedure and individual risk factors.
Infection: If the patient does not have an infection peri-operatively, signs of new infections due to surgery usually take some days to develop. Thus, a developing infection may not being evident upon discharge or by telephone call the day after. Although patients usually readily recognize common signs of infection such as localized pain, redness, tenderness, leukocyte secretion or generalized symptoms of fever; they should be informed on specific signs of potential infections related to their surgical procedure. Especially important are signs of peritonitis, as this may evolve into sepsis and multi-organ failure within short time.

Minor signs of redness and white secretion superficially from a wound may be treated with cleaning, local anti-bacteriostatic liquid or ointment, or systemic antibiotics.
Ischemia: Compartment syndrome and other types of tissue ischemia will usually be evident from increasing pain and/or numbness, and should initiate immediate inspection by health care professionals.

Practical logistics
Patients are usually advised to have a responsible escort with them and at home, to not take important decisions until the day after surgery and to not drive or take alcohol sedative drugs until next day. These are good advices on avoiding any risks, but the evidence for strict practice on all these matters is not there. It may be allowed to discuss some of these issues individually, although many health care providers will stick to these rules as mandatory instructions, also for not coming into medico-legal discussions or liability if patients by themselves choose to not follow such advice.

For more extensive reading and references recent textbooks may be recommended (28,29)

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ANESTHESIOLOGY 2017
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Protecting the Brain: Circadian Rhythms and Sleep Hygiene in the Perioperative Period

John Anderson-Dam MD **Los Angeles/CA**

Introduction

It has long been known that living things have 'intrinsic clocks' that help synchronize life to the Earth's rotation around the sun. This was first discovered in plants in the 1700's, and later recognized in humans in the 1960s.[1] By barricading a group of humans in a bunker without external cues, it was revealed that human beings have an intrinsic 25 hour clock.[1] Circadian rhythms are intrinsic and exist outside of external cues.

It is clear that the day is 24 hours. Anyone who has moved to a new time zone, also understands that circadian rhythms can be reset. The term 'zeitgebers' (German for synchronizer) is used to describe exogenous stimuli that help synchronize the body to the external environment.[1] This synchronization is termed circadian entrainment.

There are both circadian rhythms to human disease, as well as effects of circadian disruption on disease. The most common example of circadian rhythms and disease is the early morning peak in myocardial infarctions. This peak coincides with the peak in lipoprotein and fibrinogen levels.[2] The afternoon peak in sudden cardiac death and stroke correlates with peaks in platelet count.[2] Sleep disruption has been shown to correlate with development of obesity and diabetes mellitus. Sleep restriction for one week can lead to impaired insulin sensitivity.[1] Sleep disruption is a common component of systemic disease.

The goal of this course is to discuss the interplay of anesthesia and surgery with circadian rhythms and sleep disturbances. We will then introduce possible interventions that you can use to improve your patients' outcomes.

Effects of Circadian Rhythms on Anesthetics

Chronopharmacology studies the influence of administration timing on pharmacologic effectiveness. There are pharmacokinetic and pharmacodynamic effects due to the interplay of drugs with circadian rhythms.[3]

Local Anesthetics

Local anesthetic toxicity, duration of action and effectiveness all have circadian rhythms. In mice, local anesthetic toxicity has been shown to have diurnal variability.[3] Based on time of day, the percentage of mice that seize for a given dose of local anesthetic varies; the dose needed to induce a seizure varies by 30%; and time to onset of a seizure varies by almost 40%.[3] In laboring women, the duration of analgesia for a given dose of ropivacaine is 117 minutes during the afternoon and only 91 minutes overnight.[4] Intrathecal bupivacaine has a 25% variability in duration based on time of day.[4]

The underlying science of this variability is likely due to both pharmacokinetic and pharmacodynamic changes. Plasma concentrations after a single dose of lidocaine varies by time of day.[3] Clearance of bupivacaine during continuous epidural infusion varies by 60% with circadian rhythm.[3] Plasma membrane permeability to local anesthetics changes independent of plasma concentration variability.[3]

General Anesthetic Agents

The studies that exist for general anesthetic agents show that duration of activity is increased during night time and the dose necessary decreases overnight.[4] The data, while primarily for mice, show that the MAC of halogenated agents decreases and the efficacy of intravenous anesthetics increases during the equivalent of night time for humans.[4]

Muscle Relaxants

Pancuronium requirements have been shown in both humans and mice to vary in efficacy depending on the time of day.[3] This is likely related to the fact that renal and hepatic elimination are both under the influence of circadian rhythms.

In practice, the circadian effects on anesthetics themselves can be easily overcome. Neuromuscular blockade can be monitored. General anesthetics are dosed on an effect curve for every patient. Patient controlled epidural infusion pumps can be used to allow for adaptation to the patient's changing responsiveness.

Effects of Surgery and Anesthesia on Circadian Rhythms

Both anesthesia and surgery disrupt the circadian system. Most anesthesia is paired to a medical procedure. These procedures vary in degree of complexity, intraoperative, and postoperative course. Environmental factors (social cues, activity, light, noise, etc.) disrupt the normal circadian entrainment.

The cleanest data on the effect of anesthesia on circadian rhythms come from propofol anesthesia for colonoscopy. In this settings, there should be little residual effect of the procedure and the normal environmental cues are disturbed minimally. Afterwards, nighttime sleep remains constant while daytime sleep increases for two days.[5] In healthy volunteers, propofol anesthesia significantly increases sleep latency the first night after infusion.[5] In mice, propofol has been shown to shift the main circadian rhythm and the length of time for circadian entrainment afterwards differs is dependent on the time of day it is infused.[6] The data is clear that the drugs that we use disrupt our patients' sleep.

The combination of anesthesia with a surgery will further disrupt natural circadian rhythms. For surgeries ranging from arthroscopy to cardiac surgery, melatonin secretion has been shown to decrease after surgery for several days.[7] Not only is melatonin secretion diminished, but the timing of its secretion is also disrupted.[7] This disruption occurs with both propofol and halogenated agents.

Sleep Hygiene in the Perioperative Period

Both medications and surgery disrupt our patients' sleep. This is due to disruption of their internal circadian rhythms as well as ongoing environmental disruption. The question is what can be done to improve their experience and outcomes.

Melatonin is the most obvious target of pharmacologic intervention. It is one of the primary hormones released by the body to regulate sleep, and is clearly disrupted by surgery and anesthesia. There are multiple trials now registered for the use of melatonin in the ICU and postoperative period that hopefully will elucidate its optimal use moving forward. For now, there are small amounts of promising data for its use.

In humans, melatonin has been used to decrease anesthetic requirements as a pretreatment without increasing PACU length of stay.[7] In rats, melatonin acting on melatonin receptors in the hippocampus decreases post-isoflurane cognitive dysfunction.[8] In human children, oral melatonin pretreatment reduced the incidence of emergence agitation.[9] Patients over 65 years of age undergoing hip arthroplasty who were given low dose melatonin the day before surgery and into the postoperative period have preservation of MMSE (mini-mental status examination) scores compared to placebo.[10] Bariatric patients given 5 mg of oral melatonin the night before surgery and

immediately preoperatively have improved postoperative quality of recovery , pain, and sleep scores on the first night.[11] It is difficult to assess just how early we can start sleep hygiene for our patients with melatonin. The benefits are likely pleotropic, and its use as a neuroprotectant is exciting, but only speculative.

The postoperative environment can be extremely disruptive to natural sleep. In normal volunteers subjected to a simulated ICU environment, sleep is greatly disturbed. This can be improved subjectively and through polysomnography by the utilization of melatonin.[12] The biggest improvement in these volunteers was in the number of nighttime awakenings. This same effect on awakening has been confirmed in post-breast cancer patients.[13] In a randomized trial after laparoscopic cholecystectomy, patients given melatonin had improved sleep latency.[14] Patients only experienced subjective sleep improvement when they had lower than median pain scores. Melatonin use in the postoperative period could both be used for correction of a disruption of circadian rhythms as well as to overcome environmental barriers to sleep.

The simulated sleep study cited earlier also noted that the sleep disruption due to noise and light could be overcome with earplugs and eye masks.[12] This simple, cost effective treatment has been shown effective in a small PACU trial.[15] Patients had improved sleep quality and decreased morphine utilization. Another small trial utilized these interventions to improve sleep quality in ICU patients.[15] Interestingly, this trial showed that despite improved sleep quality, the disturbances in melatonin levels persisted. Another study showed disruption of sleep and nighttime awakenings increased postoperative cognitive dysfunction, but was not correlated with decreased melatonin levels alone.[14] This confirms that the disruption of sleep in our patients is multifactorial and likely requires both restoration of disturbed circadian rhythms along with environmental improvement.

Although we are used to interventions with medications and devices, altering noise and light exposure itself is likely as beneficial as barriers against it. Noise is identified by patients as a barrier to sleep.[17] An interesting trial showed a correlation between overhead announcements at night and subsequent PVCs and cardiac arrests the next day.[18]

A comprehensive program that ensures adequate analgesia, limited noise and light exposure, barriers to environmental disruption, and melatonin will likely lead to the most profound improvement in patient outcomes.

Summary

Our bodies synchronize activity to the course of the day. Disruption of sleep and these rhythms intertwines with health and disease. Anesthesia and surgery disrupt both circadian rhythms and sleep. These disruptions will affect our patients' experience and their outcome. Both pharmacologic interventions as well as environmental interventions are likely to improve these disruptions and benefit your patients.

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Enhanced Recovery After Surgery in Infants, Children and Adolescents (ERAS): A Multimodal Approach to Pain Management

Charles Berde, MD, PhD Boston, MA

A. Learning Objectives:

1. Outline a roadmap for pediatric ERAS based on adult outcomes research.
2. Review roles of multiple components of pediatric ERAS: pre-op preparation, regional anesthesia, adjunctive medications, opioid sparing, early mobilization, home transition.
3. Survey the status of pediatric ERAS programs for specific patient groups
4. Evaluate challenges and barriers to ERAS that are uniquely pediatric.
5. Consider the role of ERAS in the pediatric surgical home
6. Outline the tension between standardized care and personalized care.
7. Propose future directions for pediatric ERAS research.

B. ERAS in Adults

Enhanced Recovery After Surgery (ERAS) programs in adults arose from the pioneering research, vision, and advocacy of Henrik Kehlet and his collaborators. Peri-operative care is regarded as a form of acute rehabilitation aimed at accelerating recovery and preventing or diminishing patterns of disability and complications that have traditionally occurred after surgery. Disability is exacerbated by immobility, catabolism, inflammation, delayed enteral feeding, bowel dysfunction, over-hydration, and by traditional practices and dogmas. Pain treatment can be a double-edged sword. While better analgesia can accelerate rehabilitation, improve sleep, and blunt stress responses, analgesics can generate risks and side-effects that can impede recovery. In particular, opioids were identified as contributing to peri-operative disability and delayed recovery, and multi-modal opioid-sparing analgesic approaches were advocated.[1-8] The term "multi-modal analgesia" implies combinations of agents acting on different targets.

Through the 1980s-2000s, a series of prospective clinical trials challenged many prevailing beliefs and practices regarding postoperative care, and provided evidence for a number of individual practice changes that were associated with accelerated and/or improved recovery. Many traditional practices were shown to provide no benefit or even harm. Examples of harmful traditions included routine bowel preparation, prolonged fasting, routine and prolonged use of nasogastric tubes and bladder catheters, enforced bed rest, and treatment of anesthetic induced hypotension with fluid boluses rather than vasopressors. Beginning with colorectal surgery and then extending into other adult surgical conditions, collaborating groups developed a series of care bundles and a program for ongoing collaboration and assessment. The ERAS Society was formed to foster a multicenter continuous quality improvement effort for many types of surgery. Care bundles were developed for multiple types of surgery, with approximately 20 elements that span preoperative, intraoperative and postoperative care.

ERAS is not simply about selection of particular medications, fluid management strategies, or surgical techniques, rather it involves an overall team-based collaborative approach to care and continuous quality improvement. The patient is an active participant, not a passive bystander.

C. Bundles: the Good, the Bad, and the Muddled

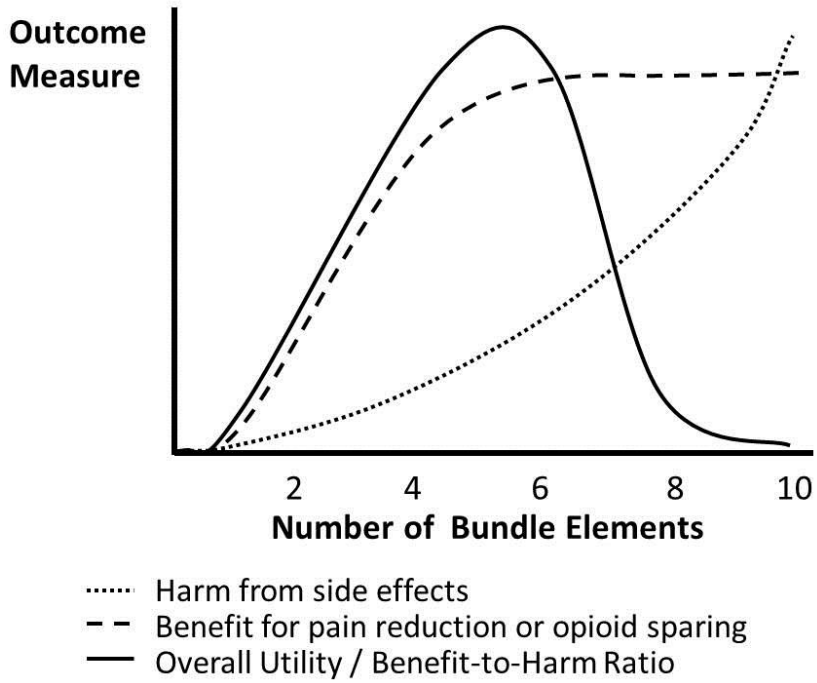
A care bundle is defined by the Institute for Healthcare Improvement (IHI) as "a structured way of improving the processes of care and patient outcomes: a small, straightforward set of evidence-based practices — generally three to five — that, when performed collectively and reliably, have been proven to improve patient outcomes." [9] Care bundles have had notable successes; commonly cited examples include: reducing central line infections, ventilator associated complications, sepsis, and obstetric / perinatal complications, improving surgical safety in developing and

developed countries, and in prolonging life in patients with cystic fibrosis. As noted by IHI, care bundles should ideally involve individual components that are each supported by Level 1 evidence. .

Care bundles do seem to offer great benefits. Are the potential downsides? First, even if several components of a proposed bundle are supported by strong evidence, it does not necessarily follow that these components will provide additional benefit when combined. In outcomes research and implementation science, particularly when considering care bundles, there is a crucial role for assessing balancing measures along with primary outcome measures, and this seems especially relevant when considering multi-modal analgesia. The presumption is that analgesics acting on multiple targets will provide additive or supra-additive pain relief, while avoiding some of the dose-limiting side-effects or toxicities of higher doses of each single agent, analogous to combination chemotherapy regimens for cancer. Consider the following example of a proposed multi-modal analgesic bundle.

Suppose that you are approaching a particular type of surgery for which previous single-intervention clinical trials showed level 1 evidence for meaningful benefit of gabapentin, low-dose ketamine, acetaminophen, NSAIDs, and wound infiltration on postoperative pain scores, nausea and vomiting, opioid use, length of stay, patient experience measures, and rehabilitation. (Each of these treatments showed significant efficacy in multiple single-treatment RCTs against placebo.) Based on this literature, you now propose to study a hypothetical multimodal protocol with 4 treatment groups: 1. Gabapentin alone, 2. Low dose ketamine alone, 3. Gabapentin-ketamine combination, and 4. Placebo. All 4 groups get acetaminophen, NSAID, and local anesthetic wound infiltration. Your findings might be the following: a. with acetaminophen, NSAID, and wound infiltration for everyone, groups 1 and 2 show smaller effect sizes for pain scores against group 4 than in previous single-treatment trials, due to the strong benefit of wound infiltration, NSAID, and IV acetaminophen, b. patients in group 3 have marginally better pain scores or marginally reduced opioid use compared to other groups, but MUCH greater delirium, somnolence, poor ambulation and frequent falls. Note that gabapentinoids can generate an adverse pharmacodynamic interaction with opioids, i.e. increased somnolence and respiratory depression[10], so that opioid-sparing per se does not guarantee a reduction in adverse events. Note also the general problem with studying incremental improvements: it's likely that subsequent add-on therapies will have smaller effect sizes compared to the initial "low hanging fruits". The preceding paragraph is not meant to discourage use of care bundles in general or multi-modal analgesic bundles in particular, only to point out that they can be complicated to study, and more is not always better.

Figure 1 depicts a rough heuristic model of how adding more bundle elements to a multi-modal regimen might not always result in additional benefit over harm.



D. Standardized versus Personalized - Are They Incompatible?

The adult ERAS consortium has generally espoused the view that, for each type of surgery, best approaches can be identified, and care should be standardized. Standardization is a common theme in the quality movement, and in several "philosophies" arising from manufacturing and operations research, e.g. Toyota processes, Six Sigma, Lean, Lean Six Sigma, High Reliability….

Standardization has many advantages. Conversely, while one Toyota Corolla engine or chassis is nearly identical to the next one in the assembly line, two patients having the same operation vary in a number of clinical, genetic, and psychological domains that can dramatically influence outcome. Stated another way, the best bundle for one patient might not be the best bundle for another patient. Among adults undergoing surgery, a number of genetic, clinical, and psychosocial variables account for considerable variance in postoperative pain severity, opioid use, length of stay, and rehabilitation outcomes. Patients with chronic pain, longstanding opioid use, catastrophizing, anxiety, and depressed mood may benefit from some additional tailored interventions that would be unnecessary for patients without these characteristics. For example, Brummett and Clauw have described features denoted as "fibromyagia-ness" that predict greater pain severity, greater opioid use, or worse rehabilitative outcomes among adult surgical patients.[11, 12]

E. What are the Overlaps and Interrelationships Among ERAS, Primary Care/Medical Home, Perioperative Surgical Home, Acute Pain Services, Regional Anesthesia Services, and Preoperative Clinics….?

To quote the late Speaker of the U.S. House of Representatives Thomas "Tip" O'Neill, Jr., "All Politics is Local." In a word, it's complicated and controversial. [13-16] Local factors will influence the composition of teams, the champions and leaders, and the roles of participants. What works best for a large pediatric service in a tertiary children's hospital might not be optimal for a small pediatric service in a general hospital. Adding new layers, new teams, and more hand-offs does not necessarily add value. In the live lecture, there will be some examples and opinions.

F. Pediatric multi-component ERAS Studies to Date

Pediatric literature on multi-component ERAS is relatively limited and preliminary. Many quality improvement efforts may not be formally named as ERAS-like, and may escape medical literature search under those keywords. Overall, there is considerable support in pediatric literature for multiple individual components of the ERAS program, but much less evidence for comprehensive bundles in pediatric surgical care.

Individual components of perioperative care that have favorable pediatric studies (either alone or as part of a bundle) include: minimally invasive surgical approaches for several types of operations, limiting or omitting extensive bowel preparation, early enteral feeding, early removal of urinary catheters, prophylactic anti-emetics, several blood conservation strategies, and early mobilization. [17 -33]

An extensive body of pediatric RCTs provide support for analgesic efficacy and/or opioid sparing from a wide range of individual systemic analgesics and regional anesthetic interventions. These include studies of acetaminophen and NSAIDs by multiple routes of administration, a range of peripheral nerve blocks, single shot caudal blocks, and continuous peripheral or epidural infusions. [34, 35, 36] Opioid sparing is a useful pragmatic surrogate endpoint for pediatric analgesic trials. [34]

What about pediatric studies of multi-modal analgesic combinations? Acetaminophen-NSAID combinations have evidence for efficacy and effectiveness[37-38]. Multiple pediatric studies support additional benefit of oral, parenteral or rectal NSAIDs when combined with regional anesthesia, either via wound infiltration, peripheral block, or caudal block[39-40]. Studies of additives to caudal local anesthetics have shown mixed results. Although clonidine and other additives do prolong analgesia in multiple studies, the extent of prolongation has been quite variable, and the optimal dose remains a matter of dispute. [41] Dexamethasone has impact in prevention of nausea, but systematic reviews found at most very modest impact on analgesia after tonsillectomy. Adult studies indicate that dexamethasone prolongs peripheral nerve blocks either by perineural administration or when administered systemically. At Boston Children's Hospital, it is common practice to administer dexamethasone intravenously for many groups of patients having peripheral nerve blocks. Pediatric studies to date of gabapentin and low-dose ketamine as add-on components of a multi-modal regimen have yielded mixed results. [42-45]

Preoperative preparation programs have demonstrated effectiveness in reducing perioperative anxiety and preventing adverse postoperative behavioral sequelae[46-49]. Preparation should be individualized in several domains, as outlined previously[47-49]. Additional studies are needed to better define roles of preoperative education, parental guidance, fear reduction, and positive coping in pediatric ERAS programs for specific types of surgery and for children of different ages and with different comorbidities. It seems plausible that web-based programs and tele-health programs will emerge as cost-effective approaches to pre-operative preparation.

Recent reviews[21-22] and recent lectures[18-19] by Brockel at the Society for Pediatric Anesthesia and Society for Pediatric Pain Medicine have attempted to survey the literature to date on pediatric multi-component ERAS programs. Shinnick et al included articles in which at least 4 of the 20 ERAS Society elements were implemented.[21] They found 5 such studies, including 1 retrospective and 4 prospective cohort studies. Several methodologic limitations were identified.

Scoliosis Surgery

Traditionally, adolescents undergoing scoliosis surgery had a prolonged course of recovery and the highest postoperative opioid utilization among all pediatric operations. Two groups have recently reported on outcomes of ERAS programs for posterior spine fusion for adolescent idiopathic scoliosis, using slightly different care bundles. Muhly et al[33] reported on a program at Children's Hospital of Philadelphia with multiple components, including intraoperative IV methadone, addition of gabapentin and ketorolac, early conversion from PCA to oral opioids, accelerated ambulation, and early removal of tubes. Average length of stay was reduced from 5.7 days to 4 days after implementation of this pathway. Thomson et al reported on a similar program for scoliosis surgery at Children's National Medical Center in D.C. as part of a perioperative surgical home framework.[16] Components of their care bundle included: limiting crystalloid infusion, blood conservation and minimizing transfusion, pre-operative laxative regimen, intraoperative dosing of either IV methadone or intrathecal morphine, prevention of

hypothermia, early removal of tubes and lines, early conversion to oral opioids, and early mobilization. In their series, median length of stay reduced from 5.2 to 3.4 days after implementation.

Urologic Surgery [26,50]

Pediatric urology practice has increasingly emphasized minimally invasive approaches, earlier removal of catheters, earlier mobilization, and emphasis on non-opioid analgesia, including NSAIDs, regional anesthesia, and selective use of anti-bladder spasm medications. Durations of hospital stay for pyeloplasty, ureteral reimplantation and hypospadias have been steadily reduced over the past 20 years.

Appendectomy[28]

Duration of hospital stay has been steadily reduced for both non-perforated and perforated appendicitis. There is support for non-opioid analgesia, avoidance of nasogastric tubes, and early feeding[28]. Hospital stays of 1 day are now common for uncomplicated appendicitis. A majority of children with uncomplicated appendicitis can be comfortable postoperatively with very sparse opioid dosing; recent records at Boston Children's Hospital recording a median of 1 prn opioid dose.

Colorectal Surgery[17, 20-24, 29-31,51]

Traditionally, children undergoing colorectal surgeries at many pediatric centers had extensive bowel preparation, prolonged fasting, prolonged use of naso-gastric tubes and bladder catheters, and little emphasis on early mobilization or early enteral feeding. Several groups in Europe and in the U.S. have reported on multi-component programs for accelerated recovery after pediatric intestinal surgeries. [17, 20-24, 29-31,51]. Much of the emphasis in these reports has been on nutrition, removal of tubes, fluid management, mobilization, and minimally-invasive surgical approaches. Opioid sparing analgesia has been a common theme.

Orthopedic Surgeries on the Extremities

Regional anesthesia has an increasingly central role in facilitating accelerated recovery for pediatric extremity surgeries. As an example, at Boston Children's Hospital, with a very pro-active regional anesthesia program, over the past 15 years, anterior cruciate ligament repair has changed from routine overnight admission to > 95% day surgery.

G. Should ERAS Efforts Focus on Healthy Children or Medically Complex Children?

My view is "both". Common operations in relatively healthy children afford opportunities for standardization,, and small increments in length of stay can have significant impact on overall health care costs. As examples, care bundles for tonsillectomy, adenoidectomy, ureteral reimplantation, pyeloplasty, and hypospadias repair have all resulted in meaningful reductions in length of stay and cost savings. Overall, these reductions in hospital stay and costs have been achieved without incremental increase in readmissions or risk.

Conversely, children with medical complexity, especially those with neuromuscular and developmental conditions, have frequent and prolonged hospital admissions for both medical and surgical diagnoses. These patients have relatively high frequencies of complications and prolonged hospital stays following scoliosis surgery[52]. Chronic respiratory dysfunction, epilepsy and bladder dysfunction were identified as comorbidities with strong associations with prolonged hospital stay and increased costs. Overall, hospital readmissions are relatively low frequency events following most pediatric operations. Structured follow-up interventions might prevent some pediatric readmissions. [53]

Children and adolescents with psychiatric illness have longer than expected hospital stays, higher opioid use, and higher pain scores following surgery. [54]

H. How Should Pediatric ERAS be Implemented and Studied?

Progress is likely to come from both "bottom-up" and "top-down" efforts, i.e. a blend of innovative pilot projects from single institutions with highly integrated multidisciplinary teams along with larger multicenter efforts with backing and funding from national or international organizations. In my view, it will be helpful for our national and international organizations (a partial list includes: Society for Pediatric Anesthesia, Society for Pediatric Pain Medicine, American Academy of Pediatrics Section on Anesthesiology and Pain Medicine, European Society of Paediatric Anaesthesiologists, Association of Paediatric Anaesthesiologists of Great Britain and Ireland, …) to dedicate resources to support partnerships with the ERAS Society and with a range of national and international pediatric surgical societies. Some of these collaborations are in progress already; for example, between the American Academy of Pediatrics Section on Anesthesiology and Pain Medicine and the American College of Surgeons National Surgical Quality Improvement Project Pediatric (ACSNSQIP-P).

I. Conclusions

Pediatrics ERAS programs are in early stages of development but are likely to make progress by following the basic principles described by Kehlet and other pioneers of ERAS in adults. There are age-related differences in physiology, in metabolic and inflammatory responses to surgery, in diseases, comorbidities, and surgical diagnoses, and in the child's understanding and ability to participate actively in their recovery. Implementation, research, and measurement should follow best practices. It will be crucial to understand how better to engage the family and the child as partners in these efforts, and to measure success both in terms of costs, resource utilization, and consensus outcome measures, but also in terms of the child's and family's experience of care[55].

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Hazards of the Anesthesia Workstation

James B. Eisenkraft, M.D. **New York, New York**

The term *anesthesia workstation* is defined as a system for the administration of anesthesia to patients and consists of the anesthesia gas supply device, anesthesia ventilator, monitoring devices and protection device(s).[1] Failure of the delivery system is a rare cause of anesthesia-related injury to, or death of, a patient. Much more commonly the delivery system is misused, the anesthesia caregiver makes an error, or the delivery system fails while the user is unaware that a failure has occurred. This lecture reviews the types of failures and complications that can occur with delivery systems for inhaled anesthetics.

Critical Incidents

The critical incident (CI) technique was first described by Flanagan in 1954[2] and was developed to reduce loss of military pilots and aircrafts during training. It was modified and introduced into anesthesia by Cooper *et al.*[3] who interviewed staff and resident anesthesiologists in a large metropolitan teaching hospital. They collected and analyzed 1089 descriptions of CI's during anesthesia.[4] A mishap was labeled a CI when it was clearly an occurrence that could have led, if not discovered or corrected in time, or did lead to an undesirable outcome, ranging from increased length of hospital stay to death or permanent disability. Other CI study inclusion criteria were: that each incident involve an error by a member of the anesthesia team or a failure(s) of the anesthetist's equipment to function properly; it occurred during patient care; it could be clearly described; and the incident was clearly preventable.[4] Of the 1089 CI's, 70 represented errors or failures that had contributed in some way to a "substantive negative outcome" (SNO) defined as mortality, cardiac arrest, canceled operative procedure, or extended stay in the PACU, ICU or in the hospital. While 30% of all CI's were related to equipment failures, including breathing circuit disconnections, misconnections, ventilator malfunctions, and gas flow control errors, only 3 (4.3%) of SNO incidents involved equipment failure, suggesting that human error was the dominant problem. Although equipment failures rarely cause death, CI's related to equipment are common and have prompted improvements in equipment design, construction, monitoring and alarms.

In 1993, the Australian Anaesthesia Patient Safety Foundation published results of the Australian Incident Monitoring Study (AIMS) that had collected 2000 CI's.[5] Of these, 177 (9%) were due to equipment failure in general and 107 (60%) involved the anesthesia delivery system.[6]

Adverse Outcomes

An accurate estimate of the number of critical incidents and adverse outcomes related to use of the anesthesia delivery system is difficult because there is no single site to which reporting is mandated. Potential sources include journal case reports, newsletters (apsf, ASA, AQI), FDA's Manufacturer and User Facility Device Experience (MAUDE) database, in the lay press as product liability litigation. Equipment failures leading to malpractice litigation in the United States has been studied by the ASA Closed Claims Project (CCP). This is a structured evaluation of adverse anesthetic outcomes obtained from the files of 35 professional liability insurance companies that indemnify approximately 50% of all anesthesiologists in the United States. A 1997 analysis by Caplan et al. of 3791 claims, [7] (76% from 1980-1990, found that GDE problems accounted for 72/3791 (2%). Of these 72, 39% were related to the breathing circuit, 17% to ventilators, 21% to vaporizers, 11% to gas tanks or lines and 7% to the anesthesia machine. Death or brain damage occurred in 76% of the 72 cases. Misuse was judged in 75% and equipment failure in only 24%. Anesthesia caregivers were considered responsible in 70% of use error cases and ancillary staff (*e.g.*, technicians) to have contributed in 30%. Predominant mechanisms of injury were hypoxemia, excessive airway pressure and anesthetic agent overdose. 78% of claims were considered preventable by the use / better use of monitoring.[8]

As of June 2017, the CCP database included 11,036 claims of which 124 were related to GDE.[8] The most recent GDE claims were for an event in 2014. Thus far, however, it appears that GDE problems are decreasing as a proportion of surgical anesthesia claims.[9] Anesthesia gas delivery claims represented 4% of surgical or obstetric general anesthesia claims from the l970's, 3% from the 1980's, 1% from the 1990s, and 1% from the period 2000-2014. There were only 24 anesthesia gas delivery system claims from 2000-2014. These include 9 vaporizer problems, 5 breathing circuit problems, 5 oxygen tank and supplemental oxygen line events, 3 ventilator problems, and 2 anesthesia machine problems. The outcomes in anesthesia gas delivery equipment claims from 2000-2014 seem to be less severe than earlier claims.

In 2000-2014, 46% of anesthesia gas delivery system claims resulted in severe injury or death compared to 80% in 1970-1989, p<0.001. Among the 24 claims from 2000-2014 were 7 deaths, 6 awareness claims, 7 pneumothorax claims, and 3 permanent brain damage claims. Payments reflect the lower severity of injury, with a median payment on behalf of the anesthesiologist of $250,000 in the 2000-2014 claims. Fifteen (63%) of the 24 post-2000 claims resulted in payment on behalf of the anesthesiologist.[8]

Over the last two decades the GDE system has undergone significant improvement as a result of advances in technology, engineering, and understanding of human factors. Anesthesia machines that lack modern safety features have been withdrawn from clinical service based upon criteria presented in the ASA Statement on Machine Obsolescence.[10] Workstation manufacturers and regulatory bodies are constantly striving to increase patient safety by improving designs according to the following fundamental principles:

1. Designs to prevent error (e.g., pin-index and diameter indexed safety systems for medical gases); Menu-driven and automated pre-use checkouts might also be considered in this category.
2. Designs to correct for use(r) error, such as O2/N2O proportioning systems ensure that ≥ 25% O2 is delivered in an O2/N2Omixture; high pressure relief valves in the breathing system to prevent positive pressure barotrauma if an excessive TV or pressure is set on the ventilator.
3. User-friendly monitors of delivery system function (pressure, volume, flow, respiratory gas composition) as well as monitors of patient physiological function to detect possible problems that may be delivery system or patient related.
4. User-friendly integrated prioritized alarm systems that alert the anesthesiologist when parameter limits are not met or are exceeded.;
5. Education /simulation to provide a focused response to alarm situations to prevent adverse outcomes.[11]

Anesthesia Practitioners and Fault-finding

Anesthesia caregivers have performed poorly in studies where they are presented with faulty equipment to troubleshoot.[12],[13] Many contemporary workstations incorporate computer-assisted self-tests that automatically perform a part of the pre-use machine checkout. The availability of such automated checkout features further adds to the complexity of constructing a uniform pre-use checklist such as that published by the FDA in 1993.[14] In 2008 the ASA published recommendations for pre-anesthesia checkout of machines, taking into consideration newer workstations that perform automated checkouts. [15] The ASA guidelines present a template for departments and practitioners to design pre-anesthesia checkout procedures specific to their needs and equipment. Sample checkout procedures that are workstation model-specific have been developed by individual departments and are available on the ASA website (http://www.asahq.org). The reader is encouraged to review the checkout guidelines and to understand the rationale for, and importance of, each step.

Hazards Associated with Components of the Anesthesia Gas Delivery System

Gas supplies.

Gases may be supplied from hospital pipelines, large cylinders and backup tanks workstation. A reliable supply of O2 is essential yet pipeline failure (no gas) and delivery of the wrong (hypoxic) gas have been reported.[16] An O2 analyzer monitoring the patient's FiO_2, with functioning low concentration alarm is crucial. Also, recognize that there is no **qualitative** O2 analyzer between the wall outlet or tanks and the workstation. Only the gas in the breathing system is analyzed, but not the gas delivered from an auxiliary O2 workstation flowmeter or one connected directly to a wall outlet. In one case two patients died when an O2 flowmeter was connected to a wall N2O outlet.[17] Realize that if the O2 pipeline delivers a hypoxic gas that same gas will be delivered from the auxiliary O2 flowmeter to which nasal cannula may be connected, and to any auxiliary 50 psig DISS oxygen take-off connector (e.g., for a Sanders type emergency jet ventilator). In a lab study in which O2/N2O pipeline crossover was simulated, many participants believed that the auxiliary O2 flowmeter would still deliver O2.[18]

The anesthesia workstation must have a backup supply of oxygen, usually from a tank of oxygen mounted in the hanger yoke and ready for use with the tank-key present. The anesthesiologist must be trained to replace an oxygen tank if necessary. In one study, many residents were deficient in this (taken-for-granted) simple skill.[19],[20]

In the event of an oxygen pipeline problem, the pipeline hose to the workstation must be disconnected in order for O2 to flow from the backup tank. It is generally assumed that in the U.S. all O2 tanks are green in and that the PISS will ensure that only an O2 tank can be mounted in the hanger yoke for O2. In fact there is no FDA standard for cylinder colors so it is important to read the tank label.[21] Also the PISS can be defeated if yoke pins are removed or several washers (Bodek seals) are placed between the tank and hanger yoke.

Most medical gas hoses connect to wall outlets via a gas-specific "quick connect" system. that are also manufacturer-specific. There is a report of ancillary staff connecting the machine N2O hose to a wall CO2 outlet leading to hyperventilation and hypercarbia.[22] This was possible because in that manufacturer's quick connect system

the N2O and CO2 connectors were mirror images of each other; by rotating the N2O connector through 180 degrees it was possible to connect it to the CO2 outlet. There are also reports of water being delivered via the air pipeline and filling the rotameter tubes with water when the air flow control valve is opened.[23] This is caused by failure in the drying system in which the compressed air is prepared.[24]

Anesthesia workstation problems

There are relatively few cases of machine-related adverse outcomes in the ASA Closed Claims database. There are a number of case reports of problems with contemporary workstations, almost all of which have been use(r) errors rather than machine failures. Many would have been preventable by a properly performed pre-use checkout. In an effort to ensure that the pre-use checkout is performed correctly, workstation manufacturers have automated the process as much as possible. This facilitates more frequent checking, optimizes the process, allows others to perform the checkout, allows the caregiver to see the status, and maintains a log. Not all of the checkout procedures can be automated, however, therefore certain steps must be performed manually. Of particular importance is to ensure that the breathing system is correctly assembled, connected and that the CO2 absorbent is present and satisfactory. The breathing system function can be tested by connecting a second reservoir bag to the Y-piece to act as a model lung. One then ventilates the model lung manually using the circuit reservoir bag and then mechanically using the ventilator. The breathing circuit unidirectional valves should be checked for presence and proper operation during the respiratory cycle. Some anesthesiologists prefer to check the circuit function by breathing through it themselves; while not the most hygienic method it is likely more sensitive to detect partial obstructions.[25 26 27]

Contemporary workstations are computerized and therefore dependent on a supply of electricity. They should be connected to the emergency electrical outlets in the OR, i.e., those that will receive power from a backup generator if the main power is interrupted. The workstation also has a backup battery that will usually maintain machine and ventilator function for 30-40 minutes; the physiologic monitoring systems, however, may not be powered by a backup battery. There should be a plan in place of how to manage the anesthetic in the event of complete electrical failure. All contemporary workstations must have a fallback system in the event of electrical power supply failure. Some workstations (e.g., Drager Apollo) can deliver anesthesia as long as there is a supply of compressed gas because they have mechanical needle valves, rotatmeter flowmeters, and mechanical vaporizers (except for desflurane). Ventilation may have to be spontaneous or manual, rather than mechanical if the electrical power fails.

In the Dräger Fabius workstation, individual gas flows are controlled by mechanical needle valves and measured electronically. The gas mixture created (O2, N2O, air, agent) then flows through a mechanical rotameter (glass tube and bobbin) en route to the breathing system. A case is reported where gas flows were set, measured electronically and displayed digitally but the mechanical total gas rotameter showed zero flow to the breathing system.[28] This was due to a leak just upstream of the total gas flow rotameter. The authors conceded that a complete pre-use checkout would have detected the leak.

The GE Aisys workstation uses an electronic gas mixer for O2, N2O and air as well as an electronic vaporizer (Aladin) system. In the event of a complete power failure, this workstation cannot supply an anesthetic gas mixture; only oxygen can be delivered to the breathing circuit from a backup mechanical (alternate) flowmeter.[29] Anesthesia must then be maintained using iv agents.

Anesthesia Vaporizers

The ASA 2013 CCP update[10] found that of the gas delivery system claims, vaporizers were at the top of the list. Problems include leaks, misfilling, overdose, and underdose that may result in patient awareness. Leaks in a mechanical vaporizer should be detectable by a properly performed pre-use checkout of the workstation's low pressure system. Anesthesia underdose may be due to a leak, an empty vaporizer or a vaporizer that was turned off (or not turned on again after being refilled with agent). Anesthetic overdose may be due to use(r) error (concentration dial set too high) or liquid agent in the bypass caused by tipping the vaporizer or by overfilling (1 ml liquid agent evaporates to produce ~ 200 ml vapor).[30] Misfilling a vaporizer with an agent for which it was not designed can result in overdose or underdose depending upon the relative saturated vapor concentrations and potencies (MAC equivalents) of each agent. The purpose of agent specific filling devices (e.g., key fill, quik fil) can be defeated. In certain situations (e.g., medical missions) misfilling may be intentional because only one vaporizer may be available and the agent for which it was designed is not.[31] Unintended low and high vapor inspired concentrations can be detected if an agent analyzer is used and the alarm limits set appropriately. Anesthetic agent monitoring is not currently an ASA standard for basic anesthetic monitoring.[32]

Anesthesia Breathing System

The breathing system has often been the source of critical incidents and adverse outcomes. Problems include misconnects, disconnects, obstructions, fires and toxic products. Misconnects are generally due to use(r) error and

failure to understand the principles of the circle breathing system in use. The circuit should always be checked for correct assembly and function prior to use. Once checked out, changes should avoided and made only if absolutely necessary. Before checkout, the breathing should be assembled as it is planned to be used; an extendable circuit should be extended to the length at which it will be used because during checkout the circuit is pressurized to detect the presence of a leak as well as to measure circuit compliance. The absorbent must be checked to ensure that the absorber canister is in the circuit and the absorbent is fresh. Many workstations that use disposable absorber cartridges are equipped with self-sealing valves to allow the cartridge to be removed and replaced without creating a leak. If the new cartridge has a crack then a leak is introduced into the circuit.[33] A new lithium based absorbent (Spiralith™, Micropore Inc., Elkton, MD) does not have an indicator dye, and relies on breathing system inspired CO2 monitoring for determining whether the absorbent is used out.

Once the breathing circuit checkout has been completed it is inadvisable to make any changes unless they are absolutely necessary. Replacing a snap-in disposable absorber cartridge during a case is usually safe but opening an absorber canister during a case and not being able to close it creates a huge leak in the breathing system. A recent case report describes such an event in a patient whose airway was not easily accessible for connection to an Ambu bag.[34 35] In this case the expiratory limb of the circuit was detached from the anesthesia machine and connected to an Ambu bag supplied with oxygen. Ventilation via the expiratory limb of the circuit was maintained for 6 minutes while the absorber canister leak was corrected. The patient suffered no adverse outcome. The efficacy of alveolar ventilation was not reported but the PaCO2, end-tidal carbon dioxide undoubtedly were high considering that the volume of the expiratory limb of the circuit now constituted additional apparatus dead space.

It is important to have a mental model of the breathing system in use and appreciate some of the components that may not be obvious, such as the optional condenser used in the advanced breathing system of GE workstations (e.g., Aisys, Avance). The condenser has a spring-loaded push button drain valve used to drain water that has collected. A case is reported in which the soda lime absorber container was opened and refilled during a case as well as the condenser drained of water.[36] Following this there was a leak in the circle system that could not be identified so that the case was completed using a Bain circuit connected to the Aisys workstation's (optional) auxiliary common gas outlet. The leak was ultimately traced to the condenser drain valve.

Fires and toxic products (such as carbon monoxide and compound A have been reported with use of absorbents that contained a strong base (e.g., KOH).[37 38 39] Very high temperatures could be reached in the absorber when the anesthetic reacted with the absorbent. Soda lime and newer absorbents are less alkaline and less heat is generated during absorption of CO2.[40]

There has been an increase in the number of cases in (the CCP database) of direct connection of wall oxygen to the tracheal tube resulting in barotrauma and even death.[41] In one case, a patient who was tracheally intubated and breathing spontaneously was to be transferred to the PACU. Oxygen delivery tubing was taped into the tracheal tube connector to provide supplemental O2 at 6 L/min, which resulted in barotrauma and bilateral tension pneumothoraces. Insertion of a 14 gauge intravenous catheter into the second intercostal space in the midclavicular line failed to release any gas. This was because the needles used (32 mm) were not long enough to reach the pleural cavity.[42] Imaging studies of chest wall thickness at the second intercostal space in the midclavicular line have shown that a needle longer than 5 cm (maximum 8.2 cm) is needed to reach the pleural space in a substantial number of patients.[43,44] Purpose-designed oxygen delivery systems are available (T-piece); use of improvised oxygen delivery systems must be avoided.

Anesthesia Ventilators

Ventilators are integral components of the modern workstationVentilator failure has been reported but is rare.[45] In most cases use(r) error was the cause of failure to ventilate. Examples include failure to resume ventilation after a change in patient positioning, after median sternotomy, and following cardiopulmonary bypass. Furthermore, in most cases the ventilator or other alarms were disabled. Some new workstations (e.g., GE Aisys CS^2) incorporate a "Pause Gas Flow" function that allows gas flow and ventilation to be suspended for one minute; rather than turning off the ventilator or disconnecting the patient from the breathing circuit during median sternotomy.[46] Workstations that use a piston ventilator (e.g., Dräger Fabius, Apollo) have the potential to create a negative pressure in the breathing system during exhalation, when the piston retracts to refill the chamber with gas. If the pressure falls below threshold, such as when there is not enough gas inflow or the reservoir bag is empty, a valve opens to allow air to be entrained into the circuit and an alarm is annunciated when air enters the circuit in this way.

Fresh gas decoupling (FGD) circuits

The FGD circuit is designed such that gas entering the circuit during positive pressure inspiration is diverted into the reservoir bag so that the patient receives only the tidal volume intended. The Dräger Fabius and Apollo workstations use FGD and piston ventilators. Several problems have been reported:

1. Air entering circuit via a leak during expiration. In this case since air did not enter via the valve designed for this purpose there was no alarm.[47]
2. If there is a leak in the low pressure system of the workstation that permits air entry, mechanical ventilation is possible but not manual. The piston ventilator will continue to deliver the tidal volume as air.[30]
3. If the FGD valve is incompetent or absent, mechanical ventilation fails but manual ventilation is possible.[48]
4. If the expiratory unidirectional valve is missing or incompetent, mechanical ventilation is possible but not manual.[49] All of these situations were preventable if a complete pre-use checkout had been performed.

Monitoring the Breathing System

Appropriate monitoring of the patient circuit should lead to early detection of failures and enable prompt intervention before the patient suffers any harm. Aspects of the patient circuit that can be routinely monitored include pressure, volume, capnography, respiratory gas composition and gas flows. Used optimally (i.e., appropriate monitors, alarm threshold limits, alarms enabled and functioning) such monitoring should detect most errors or failures.

Appropriate monitoring of oxygen, carbon dioxide, nitrous oxide and anesthetic agent in the gas mixture at the patient's airway will alert to most gas delivery, composition, and agent dosing problems. An O2 analyzer is the most important monitor in the GDS because it is both quantitative and qualitative. Most sidestream sampling multigas monitors use a rapid responding paramagnetic analyzer that can display the FiO2 and FeO2 breath-by-breath. The O2 analyzer should be automatically enabled whenever the machine is capable of delivering an anesthetic gas mixture. Causes of inadequate oxygen concentration in the circuit include a hypoxic gas being delivered via the pipeline or tanks, disconnected fresh gas hose during use of a hanging bellows ventilator, O2 flow control valve turned off, fail-safe system failure, proportioning system failure, O2 leak in the low pressure system of the machine, and a closed circuit with inadequate O2 inflow rate.

Contemporary anesthesia workstations use sensors in the breathing circuit to measure gas flows and calculate volume. This allows display of plots of volume vs. pressure and volume vs. flow so that changes in these parameters may easily be detected. A closed flow-volume loop (i.e., expired volume = inspired volume) is a good evidence of a well positioned (non-leaking) LMA.

Alarms

Although delivery system failures, use errors and equipment failures cannot always be prevented, appropriate monitoring should facilitate detection of most such problems and permit intervention before patient harm occurs.[50] While the workstation may have passed the pre-use checkout, this does not preclude problems from arising during the anesthetic.[51] Monitoring/alarm deficiencies include absence (i.e., no monitor); non-function (i.e., monitor present but broken); and "disabled" (*i.e.*, monitor/alarm not turned on or intentionally turned off) and inappropriate alarm thresholds or audible volume settings.[52] In the AIMS study with respect to ventilation it was concluded that critical areas be doubly or even triply monitored and that monitoring equipment be self-activating. This philosophy might be equally well applied to other critical variables that are monitored. User friendly alarm setting features are important and easy bracketing of suitable limits ("Autolimits") is highly desirable, as is annunciation of adequate volume audible (*i.e.*, loud) as well as visual alerts. Some monitoring systems allow the user to silence all alarms permanently. While the occasional false alarm can be annoying, disabling/silencing of alarms is potentially dangerous.

Prevention of failures and adverse outcomes

Complications due to the anesthesia delivery system are uncommon but when they occur are usually due to use(r) error rather than actual equipment failure. User education/in-servicing is essential if sophisticated equipment, such as a new (computerized, electronic) anesthesia workstation, is to be used safely.[53] Education of medical and ancillary (nursing/technical) staff is also important because they may unwittingly contribute to the occurrence of a complication. It is essential that anesthesia caregivers understand the limitations of any automated checkout procedures and perform the manually required steps correctly. The automated checkout then pressurizes the system to measure compliance and check for leaks, but not necessarily for correct gas flow through the components. It may be possible for a breathing system to be incorrectly assembled, be gas tight, pass checkout, yet not permit any gas to flow to the patient.

A pre-use checkout of the delivery system should be developed by each department/institution to suit local needs and item #1 on any pre-use checkout should be that a backup means of ventilation (i.e., a self-inflating manual ventilation device [SIMVD] such as an Ambu bag) should always be immediately **available and functioning.** A recent study of missed steps in the pre-use checkout found that the most common item missed was the presence of a self-inflating manual ventilation device (SIMVD).[54] Testing the function of the (SIMVD during the pre-use checkout is essential. An excellent

presentation on how to properly test the SIMVD and can be accessed on the University of Florida website.[55] Occasionally, an SIMVD is found to be faulty, either not generating positive pressure when it is squeezed, or not releasing positive pressure when it is longer being squeezed. If a delivery system failure occurs, the patient's lungs can be ventilated with room air orO2 using an SIMVD. Recent studies suggest that there is an increased awareness of the importance of the pre-use checkout and management of machine-related critical incidents. One national anesthesiology board has even incorporated these into the Objective Structured Clinical Evaluation (OSCE) component of its Board Examination in Anesthesiology.[56]

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Current Concepts and Controversies in Acute Pain Management

Eugene Viscusi, M.D. **Philadelphia, PA**

Acute pain management continues to be challenging. Studies have demonstrated continued unmet needs with the majority of patients experiencing significant pain at some point following surgery.[1] Analgesic gaps (periods of breakthrough pain) continue to be a problem for most patients. The last year has brought an unprecedented focus on opioid abuse even with the short term use of opioids for acute pain. There is now evidence that the short term use of opioids following surgery in previously opioid naïve patients is associated with an increased risk of chronic opioid use.[2] There is keener attention to minimizing intraoperative opioids, opioids in the immediate postoperative setting as well as at discharge.

There is increasing awareness to opioid related side effects and the need to minimize opioids generally through the use of multimodal analgesic techniques. Opioid related respiratory depression and sleep apnea are now major considerations in the postoperative period. The recent Joint Commission Sentinel Event Alert of August 2012 highlights the need for greater caution when prescribing opioids including patient risk stratification, heightened monitoring and less reliance on opioids. At the other end of the opioid spectrum, we have the challenge of managing postoperative pain in the presence of opioid tolerance and chronic opioid use. There is also an emerging theme of chronic pain following surgery. This year also saw the publication of the combined societies Guidelines on Postoperative Pain.[3]

The Perioperative Surgical Home (PSH) is a recent and important development in our specialty. Anesthesiologists may be taking the lead in perioperative medicine but there remains controversy and competition among various specialties as to whom will take the lead. Acute pain management and the resulting outcome benefits are an integral part of the PSH.[4-6] Acute pain management services have historically done a portion of this effort as well as the creation of Enhanced Recovery After Surgical (ERAS) pathways[7] The management of acute pain with an eye to demonstrating outcome improvement will be an important part of the PSH and ERAS and a critical role for the future of anesthesiology taking us well beyond the walls of the operating room. While much of the focus of ERAS and PSH has been on cost savings, the ultimate goal is improved patient outcome and disability free recovery following surgery. Relatively simple techniques have demonstrated longer term benefits[8]

This Refresher Course Lecture will present current and emerging concepts in acute pain management, many of which remain controversial. This lecture will emphasize the impact of the operating room anesthesiologist on longer term outcome.

CDC and FDA Guidance on Opioids

Opioid associated risks are now major concerns even with acute pain and chronic non-cancer pain. CDC issued specific guidance on the use of opioids for non-cancer pain.[9]). Previously in 2013, the FDA changed the labels for extended release opioids clarifying that these potent agents are only for stable chronic pain when all other agents fail. In March of 2016, the FDA issued guidance (which will lead to label changes) for immediate release opioids which are commonly used for acute pain. Summarizing these changes, opioids are not first-line analgesics and are only for moderate to severe pain when other agents have failed. Further, the lowest effective dose should always be used. Finally, opioids are only for short term use. The prevailing theme is that the role of opioids needs to be reevaluated. Certainly much acute pain can be managed without opioids or with opioids as adjunctive agents for short periods.

Multimodal Analgesia

Historically, opioids have been heavily relied upon as single agents for postoperative pain. Opioids have been accepted as potent and effective analgesics but at the price of opioid related side effects. Patients typically balance side effects with pain relief – often requesting less pain relief rather than suffer opioid related nausea and vomiting.[10] These gastrointestinal side effects are distressing to patients and the most common reasons for refusing treatment.

Further, opioids have limited efficacy for some types of pain, particularly visceral and neuropathic pain. Acute postoperative pain is often a mixed pain syndrome with multiple components and hence may not be relieved well with opioids alone. With aggressive multimodal analgesia incorporating regional/local anesthesia techniques, opioids may be minimized and in some cases eliminated.

The concept of multimodal analgesia entered the acute pain literature in the early 1990's when Kehlet described the benefits of "balanced" analgesia.[11] Today, multimodal analgesia, the application of two or more analgesics acting at different pain pathways and by different mechanisms, is considered standard practice to enhance analgesia and minimize reliance on opioids. The ASA Guidelines on Acute Pain Management support the use of nonopioids as around the clock agents with opioids as supplemental agent. The most commonly employed agents are local anesthetics, acetaminophen, NSAIDs, COX-2 selective inhibitors, gabapentin and pregabalin, and ketamine. While these agents may be viewed as less potent than opioids, emerging information suggests they may be able to play a more significant role than previously thought.[12] Opioid reduction or "sparing" is at the heart of many of the challenges and controversies in acute pain management. Opioid reduction alone is not sufficient! True opioid sparing requires not only a reduction in total opioid but also some concomitant benefit usually observed as a reduction in opioid related side effects. Future acute pain management strategies will likely rely much less on opioids.

Opioid Related Respiratory Depression and Sleep Apnea

The effects of opioids on respiration are well known. Opioids are known to inhibit the ventilator response to both hypoxia and hypercapnea. In recent years there has been increasing awareness to critical respiratory events.[13,14] The emphasis place on "pain the 5th vital sign" by the Joint Commission several years back may have increased the use of opioids in the hospital setting in an attempt to improve pain assessments. The increasing incident of sleep apnea, often blamed on increasing obesity in our society, is also considered a risk factor for opioid use.

Obstructive sleep apnea (OSA) is usually associated with obesity, snoring or other signs of airway obstruction. Yet, the majority of patients with OSA are undiagnosed and many are not obese.[15] Further, OSA may coexist with central sleep apnea (CSA).[16] Further, it has been demonstrated that patients with OSA may develop respiratory depression from opioids but that it is in fact on a central basis and not obstructive.[15] Up to 50% of long term opioid dependent patients may exhibit CSA.[18] The severity of central sleep apnea is proportional to the daily chronic opioid dose with morphine doses greater than 200 mg/day being a significant.[19-21] Chronic opioid use reduces the proportion of time spent in REM sleep. CSA worsens during nonREM sleep further increasing the risk of a respiratory event in the chronic opioid.[22,23] Postoperative sleep-disordered breathing is now recognized as a risk factor for postoperative respiratory events. Chung and colleagues identified that at least 18.3% of non-sleep apnea patients develop moderate to severe sleep disordered breathing postoperatively.[24]

While respiratory depression (RD) is a serious problem, definitions of RD vary widely. Reported incidences range from 1% to approximately 40%.[25] However, these definitions include transient oxygen desaturation or transient respiratory rates below 10 breaths per minute. While these events should not be taken lightly, it is difficult to predict which or how many of these events will progress to *critical* situations requiring intervention. In one series of over 2000 patients with standard patient controlled analgesia settings, the incident of critical respiratory depression was 0.1-0.3%.[26] The controversy here is determining if and what type of monitoring is appropriate for patients receiving opioids and how to minimize opioid use.

An ASA task force provided guidance on managing patients with OSA.[27] There are no specific analgesic recommendations but rather favor minimal opioid use and multimodal analgesia. Local / regional anesthetic techniques are encouraged as is epidural analgesia without opioid.

There are various monitoring techniques recommended for the OSA patient but no definitive approach. Pulse oximetry is generally recommended although capnometry may be a more sensitive indicator. Observational monitoring in the PACU with an OSA prescreening tool may have a role in risk stratifying patients who would benefit from the most aggressive monitoring.[28] The STOP-Bang scoring system has also shown merit in identifying at-risk patients.[29]

Using the STOP-Bang questionnaire, one team of investigators found 41.5% of a standard preoperative elective population had OSA. These investigators also identified a ten-fold increase in pulmonary and cardiac complications in patients with OSA.[30] Clearly, patients with OSA may benefit from advance planning. Early identification is key. This allows planning an anesthetic to minimize reliance on opioids both intra- and post- operatively as well as designing an appropriate multimodal approach with appropriate monitoring.

The role of postoperative CPAP has remained somewhat controversial. Liao and colleagues found that auto-titrated CPAP in surgical patients with OSA reduced the apnea-hypopnea index (AHI) but that only 26-48% of patients used their CPAP device more than 4 hours each night.[31] In a systematic review by Nagappa, there was no significant difference between postoperative adverse events with or without CPAP although the AHI was reduced.[32]

The recent closed claims analysis identified that the vast majority of incidents occur in the first 24 hours and were deemed largely preventable.[33] Opioids were a common theme along with other nonopioid sedative agents. Continuous delivery of an opioid by infusion (intravenous or neuraxial) was a significant factor. This follows the emerging signal with extended release / long acting oral opioid formulations leading to respiratory deaths. While enhanced monitoring may reduce critical opioid events, clearly opioids are a major factor and it behooves us to minimize their use when possible.

Emerging Views on Opioids

Mu-opioid receptors are ubiquitous within the CNS and at peripheral sites. The analgesic action of opioids within the CNS is well known. Opioid adverse events are related to both central and peripheral receptors. Peripheral opioid receptors have a role in ileus, constipation, hormonal regulation, tumor growth, angiogenesis and immunological function. While long term opioid use has clear risks, there is emerging evidence that the short term use of opioids may have significant consequences. Use of opioids for as little as one month may produce lasting changes in the brain.[34] Elderly patients given opioids for postoperative pain are at risk for long term opioid use.[35]

Opioids may reduce survival after cancer surgery.[36] In retrospective studies, perioperative plans that reduce opioids have been shown to increased cancer survival following surgery for breast cancer, prostate cancer and possibly bowel cancer. These typically involve regional anesthetic techniques (paravertebral blocks, epidurals). Opioids are known to enhance angiogenesis leading to tumor growth and to inhibit the immunological response which may alter survival. Recent work in rodents with peripheral opioid antagonism demonstrated an inhibition of tumor growth.[37]

Opioid Tolerance and Hyperalgesia

Long term use of opioids is known to produce tolerance or decreased efficacy requiring dose escalation. Some patients on chronic opioids also exhibit hyperalgesia or altered pain sensitivity.[38] As a group, patients on chronic opioid therapy for pain or methadone maintenance are well known to present significant postoperative pain challenges.

There is now much clearer evidence that intraoperative opioids can contribute to tolerance and hyperalgesia .[39] Intraoperative opioids are associated with an increase in postoperative opioid requirement. Collard *et al* identified significant increase in PACU fentanyl opioid rescue use in patients receiving remifentanil or fentanyl vs. esmolol.[40] Here again, the evidence supports incorporation of nonopioid multimodal approaches and opioid reduction even during the anesthetic.

For these patients in the postoperative period, increased opioid requirements are expected but often pain is unrelieved with opioids alone.[41] Opioid tolerant patients benefit from aggressive multimodal analgesia with regional anesthetic techniques. Recently, ketamine has shown efficacy in this setting. In opioid tolerant spine surgery patients, Loftus and colleagues demonstrated that pre- and intra-operative ketamine reduced pain and opioid requirements in the immediate postoperative period and up to six weeks following surgery.[42-44] Low dose ketamine is now commonly employed in opioid tolerant patients. There is some controversy as to when and where ketamine should be administered. Loftus and colleagues demonstrated benefit from pre- and intra-operative administration. Postoperative ketamine infusion is a useful adjunct in multimodal analgesia for these patients but further studies are warranted to evaluate dosing and duration of treatment.

Chronic Pain Following Surgery

Chronic pain may be a consequence of surgery. Until recently, normal resolution of acute pain was expected to be a routine occurrence. There is a significant burden of long-term pain following surgery. The incidence following thoracotomy and radical mastectomy may exceed 50%. The incidence following inguinal hernia repair is 19-40%. There is now an understanding that healing with neuronal plasticity may occur resulting in chronic postsurgical pain (CPSP). CPSP has been linked to severity of acute pain.[45] Following thoracotomy, patients who experience pain of greater intensity and for a longer duration had a higher risk of persistent pain. Kehlet has identified not only intense acute pain but also, nerve injury and intense inflammatory response as associated factors.[46]

Surgery often results in an intense peripheral inflammatory response (peripheral sensitization) as a consequence of the release of local inflammatory mediators. This "inflammatory soup" causes peripheral sensitization leading to central sensitization (the release of central inflammatory mediators) which in turn results in further pain sensitization.[47] Even in the presence of total neuronal blockade (spinal anesthesia), there is still a central humoral response to peripheral inflammation. Hence, local anesthetic techniques alone cannot inhibit this process of central sensitization.

Total knee arthroplasty has a reported incidence of CPSP approaching 9%. A recent study utilizing a complex multimodal regimen with pregabalin for total knee arthroplasty showed a marked reduction in chronic neuropathic pain.[48] While this is one study, it provides a basis for the potential use of multimodal analgesia as an approach to reducing the prevalence of CPSP. Still, another study with chronic pain following total joint arthroplasty supports that patients may have underlying vulnerabilities such as major depression or chronic pain elsewhere.[49] There is some evidence correlating CPSP to individual pain response with experimental pain models.[50]

In a number of surgical models, perioperative pregabalin either alone or within a complex multimodal regimen has been shown to reduce pain in the immediate postoperative period and in some studies in the months following surgery.[51-56] Recently, intraoperative lidocaine infusion was shown to reduce chronic pain following breast surgery.[57]

Ultimately, chronic post-surgical pain is likely to be multifactorial in origin. Current best evidence suggests that a multimodal analgesic approach may offer the best current approach for reducing long-term pain after surgery. If specific at-risk individuals can be identified in the future, targeted approaches might be possible.

Anesthesia and Longer Term Outcome

In addition to the implications for cancer survival and chronic pain, our intraoperative anesthetic management may also influence important aspects of quality of life. A recent study demonstrated that pre-incision dosing of ketamine during on-pump cardiac surgery attenuated postoperative cognitive dysfunction. A concomitant reduction C-reactive protein was also noted.[58] Surprisingly, high-dose dexamethasone did not reduce cognitive dysfunction so this ketamine effect is not from anti-inflammatory properties.[59] Intraoperative lidocaine was shown to improve quality of life and reduce pain at three months following complex spine surgery along with a slight reduction in 30 day complications. Lidocaine, in addition to its local anesthetic properties, is known to have potent anti-inflammatory properties.[60]

A substantial body of literature supports the use of perioperative lidocaine infusions. In[1] addition to its anti-inflammatory properties, lidocaine decreases ileus, reduces opioid requirements and pain. Lidocaine is particularly effective in soft tissue injury models. In addition to improved quality of life indicators, lidocaine improves quality of recovery in laparoscopic bariatric surgery.[62]

Lidocaine exhibited potent antitumor activity in hepatocellular carcinoma by inducing apoptosis and inhibiting tumor cell migration.[63] Across multiple outcome measures, there is increasing support for the use of perioperative lidocaine.

Expanding Role for Ketamine

There is increasing use of ketamine both intraoperatively and postoperatively. While the utility of ketamine is gaining acceptance, concerns for potential side effects have limited use. Recent publications have reviewed large databases where ketamine is routinely used on standard wards, demonstrating remarkable safety compared to opioid-related side effects.[64] Other authors applaud the use of postoperative ketamine as a means to reduce the known complications of opioids in the postoperative period.[65]Ketamine has particular utility in managing patients with opioid tolerance as demonstrated in a number of studies. Of note recent studies support longer term outcome improvement. In opioid dependent spinal fusion patients, Nielson et al found ketamine improved pain control and reduced opioid use with a trend toward less persistent pain at 6 months.[66] Further, patients who received ketamine had no greater incidence of nausea, vomiting, hallucinations or nightmares.

Combined Society Guidelines

This year saw the publication of the consensus guidelines on postoperative pain from the American Pain Society, The American Society of Regional Anesthesia and the American Society of Anesthesiologists.[3] The document is highly recommended reading for anyone managing surgical patients. These evidence-based guidelines support the use of multimodal analgesia and in particular the use of intraoperative ketamine and lidocaine.

Conclusions

Acute pain management continues to be challenging. While significant strides have been made in many areas, specific patient populations and surgical pain models remain underserved. Opioid related adverse events, particularly respiratory depression are now identified for their significant impact on poor outcome. Patient satisfaction, largely driven by experience with pain and treatment side effects, is now an important component for reimbursement within the Affordable Healthcare Act. Multimodal analgesia is now recognized as a standard of care and is familiar to our surgical colleagues. The most current literature supports opioid reduction techniques and multimodal analgesia from the preoperative period and through the recovery period. Integration of multimodal analgesia into our anesthetic plan will promote early utilization both pre- and intra-operative to maximize the benefits. The emerging information on opioids suggests that these agents will likely play a lesser role in our future approaches both in our anesthetic management and for acute pain management. The role of the anesthesiologist has potentially far reaching implications on the long-term welfare of the surgical patient but only if we as a specialty embrace our role as perioperative physicians.

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Opioid and Other Substance Use Disorder in Pregnancy: *Strategies for Success*

Lisa Leffert **Boston, MA**

Despite a lower prevalence of substance abuse in pregnant versus non-pregnant women of child-bearing age, recent national statistics reveal that 4.7% of pregnant patients used illicit substances, with the highest prevalence in the youngest age group (18-25 years; 7.4%).[1] This misuse is highest in the second trimester (6.4%) and lowest in the third trimester (3.1%).[1] Depending on the substance used, there can be significant maternal, perinatal and anesthetic implications.

Opioids

Introduction

Opioid use and misuse in the United States in both the pregnant and non-pregnant populations has grown dramatically; the prevalence of opioid abuse or dependence in pregnant women was shown to have increased 127% between the years 1998 and 2011.[2] From 2002-2015, the total number of deaths in the general population from opioid overdoses increased by almost three-fold.[3] Worldwide, the United States accounts for 80% of the opioids consumed. Fentanyl and other synthetic opioids are the fastest growing sector of opioid misuse; the high potency (100x more potent than morphine) and ease of synthesis make it a particularly dangerous drug of misuse. Fentanyl is being used as an independent drug of misuse and is being mixed with heroin. A recent analysis in Canada showed that fentanyl was present in 89% of seized counterfeit oxycontin tablets.[4]

Opioids have traditionally been prescribed liberally by physicians during pregnancy for common complaints such as back pain, headache, and abdominal pain; 14.4% of pregnant women with commercial insurance[5] and 21.6% of pregnant women with governmental insurance[6] were recently found to have filled an opioid prescription in retrospective reviews. In addition, hydrocodone and oxycodone are commonly prescribed for post cesarean delivery pain management. Collectively, these medications have historically been thought of as being low risk in pregnancy. In 2016, the Federal Drug Administration (FDA) issued a back-box warning on immediate-release opioids, highlighting the risk of "misuse, abuse, addiction, overdose and death". These opioids of abuse include the non-medical use of oxycodone and diamorphine (heroin), both semi-synthetic opioids, and more recently, of the synthetic opioids fentanyl, and of the elephant tranquilizer, carbofentanyl. Other opioids of abuse include other oral or IV morphine formulations (e.g. oxycontin) and medication assisted therapies (MAT) such as buprenorphine and methadone. Crossover between prescription opioid and heroin abuse has also been observed. Studies have shown that the nonmedical use of multiple opioids has been associated with a transition to heroin and heroin users were almost four times more likely to report nonmedical use of opioids in the previous year.[7-9]

On April 20th 2017, the FDA issued an additional warning advising that breastfeeding mothers should not receive codeine or tramadol.[10] This caution was based on evidence that the use of these medications in women who are genetically CYP2D6 ultra-metabolizers can result in excessive amounts of morphine in maternal breast-milk, with the resulting potential for neonatal overdose and respiratory depression.

Further investigation has yielded insight into how changes in prescribing habits can impact maternal opioid use. A recent prospective study demonstrated that there was an association between the number of tablets dispensed and the number of tablets consumed postpartum. Women who were prescribed 31 or more opioid tablets upon discharge consumed significantly more tablets than those who were prescribed 30 or less tablets (incidence rate ratio 2.01, 95% Confidence Interval 1.48-2.76 and 1.35, 95% CI 1.10-1.65, respectively).[11] It is interesting to note that the amount of opioids dispensed was not directly related to pain control, patient satisfaction or the need to obtain prescription refills.[12]

Fetal and Maternal Effects

Opioid abuse in the antepartum period has several potential negative effects on the pregnancy. A retrospective study in women exposed to a variety of opioids in the first trimester of pregnancy suggested a higher incidence of neural tube defects (aOR: 2.2, 95% CI: 1.2-24.2).[13] Though well designed and compatible with animal

study findings, this study was subject to recall bias. In addition, pregnancies associated with opioid use/dependence during pregnancy were found to have an increased risk of cesarean section (aOR: 1.2, 95% CI: 1.1-1.3), oligohydramnios (aOR: 1.7, 95% CI: 1.6-1.9), preterm labor (aOR: 2.1, 95% CI: 2.0-2.3), and IUGR (aOR: 2.7, 95% CI: 2.4-2.9). In the same study, these pregnancies were also associated with an increased risk of an extended length of stay (aOR: 2.2, 95% CI: 2.0-2.5) and in-hospital mortality (aOR: 4.6, 95% CI: 1.8-12.1).[2]

Women who abuse opioids are more likely to engage in smoking and other polysubstance abuse, and are more likely to have concomitant infectious disease (e.g. HIV or Hepatitis B or C). As with substance abuse in general, these women often have untreated psychiatric disorders and sexual promiscuity, which leads to more frequent pregnancies. The subsequent lack of prenatal care is then associated with more frequent pregnancy complications.

Acute detoxification is generally not recommended during pregnancy, primarily due to concern for relapse, and also for maternal and fetal opioid withdrawal. The American College of Obstetricians and Gynecologists (ACOG) instead recommends medication assisted therapy with associated counseling and general prenatal care with either methadone or buprenorphine.[14] Although methadone was historically the substitution therapy of choice, the relative ease of patient access to buprenorphine (i.e. the receipt of a multi-day supply rather than a daily visit to the clinic) and the apparent decreased duration and severity of neonatal abstinence syndrome, have made buprenorphine an increasingly popular choice during pregnancy.[15] Breastfeeding is also endorsed in postpartum women who are on stable MAT program with either methadone or buprenorphine, as long as they are not using illicit substances, and are not HIV positive. Increased availability of the reversal agent, nalaxone, is credited with helping to combat the growing numbers of overdose deaths.

Anesthetic Management

The altered physiology of opioid abusing parturients and the pharmacology of their substitution therapy contribute to challenges in their peripartum anesthetic care. Whenever feasible, a pre-delivery anesthetic consultation can help to establish trust between the patient and her providers, and provide an opportunity to discuss the multi-modal menu of care options. Women who take opioids chronically are typically tolerant to the analgesic effects, likely through a combination of chronic changes in pain pathways, and, in those receiving buprenorphine, the very high μ receptor affinity of the drug. It is the competition at the μ receptor between buprenorphine and other opioids that inhibits pain management, *not* the small amount of naloxone (with low oral bioavailability) that's incorporated into suboxone to discourage intravenous injection. It is crucial that patients on MAT therapy NOT receive the mixed agonist/antagonist medications commonly used on labor floors (e.g. nalbuphine, butorphanol) as their use may precipitate maternal and fetal withdrawal.

Neuraxial analgesia for labor, or anesthesia for cesarean delivery, is highly desirable if not otherwise contraindicated. Studies show that the intrapartum pain scores for parturients on methadone and buprenorphine who received neuraxial analgesia or anesthesia are reasonably similar to their respective controls. However, post-cesarean delivery pain management needs between patient populations were dramatically different from controls not on MAT. Specifically, obstetric patients on methadone therapy needed 70% more opiate analgesic and those on buprenorphine needed 47% more opiate analgesic.[16,17] However, these patients are not necessarily tolerant to the sedative effects of additional opioids or adjunct medications, likely increasing their risk of respiratory compromise and perhaps contributing to the observed increased risk of death.

MAT or chronic opioid therapy does not contribute significantly to acute pain management, but should be maintained to satisfy chronic requirements. A patient's methadone dose should be confirmed with the primary prescriber and should only be adjusted during pregnancy in collaboration with him or her, if needed. There are several options for peripartum buprenorphine management, outlined in Table 1.

Pearls and Tips:

- Know the obstetric plan: likely vaginal delivery unless otherwise contraindicated
- Avoid other agonist-antagonist therapy
  - e.g. Nalbuphine, butorphanol, pentazocine, naloxone
- Implement multi-modal therapy (Be creative!)
- For labor:
    - Early epidural catheter placement
  - Breakthrough pain is more likely a sign of an ineffective epidural catheter, as with any patient
  - For post-cesarean delivery pain management:

- Include non-steroidal anti-inflammatory agents (NSAIDs) & Tylenol, routinely, as standard care
- Tranverse abdominal plane blocks or catheters may be beneficial
- Consider neuraxial opioid (e.g. duramorph) +/- local anesthetic (e.g. PCEA) for first 12-24 hours
- If elective cesarean delivery, consider "split CSE", with lumbar spinal anesthesia and low thoracic epidural catheter to facilitate PCEA for first 12-24 hours postpartum
- Consider adding low dose intravenous ketamine infusion
- Consider adding intravenous opioids (via patient-controlled analgesia), as needed, without background rate. Monitor patient closely for respiratory compromise.
- Perioperative gabapentin may have some utility in these patients at risk for high intensity post-operative pain (not investigated in this subpopulation)

If receiving adjunct medication with sedative effects (e.g. po gabapentin or epidural clonidine), patients may be at increased risk for respiratory depression.

Alcohol

Introduction

According to a recent meta-analysis, the global prevalence of alcohol use during pregnancy was estimated to be 9.8% (95% CI 8.9-11.1).[18] Withdrawal from alcohol can produce the syndrome of tremor, confusion, electrolyte abnormalities, and seizures (i.e. Delerium Tremens) which can be modulated by benzodiazepines (with or without dexmedetomidine), haloperidol, or clonidine.

Maternal and Fetal Effects

Alcohol use acts as both a stimulant and a depressant to the maternal central nervous system through a variety of neurotransmitters; endogenous opioids further reinforce alcohol use. Alcohol and metabolite (acetaldehyde) are directly toxic to the brain. Heavy consumption can lead to cirrhosis with encephalopathy, coagulopathy, and esophageal varices, each of which can complicate anesthetic management. Maternal alcohol use occurs throughout pregnancy, with the highest percentage in the first trimester (16.4%) compared to the second (6.1%) and third (4.3%) trimesters.[1] The higher likelihood of alcohol use during the first trimester of pregnancy is most likely because many women were unaware of the pregnancy at the time[19] or may not be aware of the prenatal effects of alcohol. Maternal alcohol use occurs across all races, with the highest percentage of use in 18-25 year olds (11.8%).[1]

Alcohol use causes the *single most preventable fetal birth defect*, most specifically fetal alcohol syndrome (FAS), which exceeds all other birth defects in the United States. [18] The global prevalence of FAS is estimated as 14.6 per 10,000 people.[18] Mental and behavioral disorders, chromosomal abnormalities, congenital deformities and malformations have been identified as comorbid conditions co-occurring in individuals with FAS.[20] Paternal as well as maternal alcohol use has also been associated with FAS.[19]

Anesthetic Implications

As is true in obstetrics in general, neuraxial anesthesia is preferred to general anesthesia if the patient is otherwise an appropriate candidate.

Tips and Pearls:

- Airway
  - Aspiration risk
    - Decreased lower esophageal sphincter tone
  - More colonization with pathologic bacteria
- Effect on minimum alveolar concentration (MAC)
  - If acute intoxication, decreased MAC
  - If chronic intoxication, increased MAC
    - High risk of awareness
- Effect on P-450
  - Short-term consumption- competes with P-450
  - Long-term consumption- increases P-450 (associated with decreased levels of diazepam, labetolol)

- Causes decreased pseudocholinesterase levels, although not clinically significant

Cannabis (marijuana)

Introduction

In 2015, 3.4% of pregnant women reported using cannabis in the past month, with the highest percentage during the first trimester (4.0%) compared to the second (3.5%) and third (2.7%);[1] the increase in prevalence of use among pregnant women was 62% from 2002-2014![21] Recently, synthetic cannabinoid use has been increasing, resulting in an increase in associated emergency room visits.[22]

As it is often associated with polysubstance abuse, it is difficult to separate out the cannabis-specific effects. Also, cannabis contains more than 400 compounds (>60 Cannabinoids) with THC responsible for most of psychotropic effects. Because cannabis is a highly lipid-soluble drug that is sequestered in fatty tissues, it has a long elimination half-life (7 days or 1 month for its metabolites).[23-25]

Maternal and Fetal Effects

Cannabis interacts with peripheral and central cannabinoid receptors producing psychoactive effects including primarily euphoria, anxiolysis, analgesia, and appetite suppression.[27] There is a biphasic effect on the autonomic system with low doses producing a sympathetic effect and high doses, a parasympathetic effect.[28,29] Maternal effects center primarily on disruption of the airway and lungs due to smoking inhalation. A mild maternal abstinence syndrome occurs with discontinuation of the drug. A recent meta-analysis demonstrates that women who use cannabis during pregnancy are at greater risk of anemia.[30] Synthetic cannabis use results in an acute intoxication syndrome characterized by sympathomimetic effects, including hallucinations, delirium, and psychosis. Acute renal injury, acute ischemic stroke and death have also been reported in association with its use.[22,31]

Several animal and some human studies have investigated the fetal effects of maternal cannabis use, although the conclusions are limited by confounders and possible lack of generalizability. More studies are needed to assess the maternal and fetal risks of cannabis as its use in the general population is increasing.[1] However, because of concerns for impaired neurodevelopment and smoking-related impairment, it is recommended by ACOG that both recreational and medicinal use of marijuana be avoided during pregnancy and breastfeeding.[26]

Anesthetic Implications

As is true in obstetrics in general, neuraxial anesthesia is preferred to general anesthesia if not otherwise contraindicated.

Tips and Pearls:

- Hemodynamic perturbations are typically minimal, except in the case of synthetic cannabis
  - Atropine, ketamine may exacerbate tachycardia
- If general anesthesia, expect:
  - Increased airway secretions
  - Impaired mucociliary clearance
  - Increased airway reactivity
- Produces an additive effect with other sedatives
- May have effect on pain perception[32]
  - Low dose- no effect Medium dose- decrease pain High dose- increase pain

Stimulants

Introduction

Stimulants include cocaine, and the amphetamine analogues such as methamphetamine (i.e. “speed”; methyl radical), ecstasy (“MDMA”; methylenedioxy group confers hallucinogenic effects), ɣ hydroxybutyric acid (GHB), 3, 4-methylenedioxypyrovalerone (MDPV or bath salts). These drugs of abuse are of particular interest to anesthesia providers because of their intense activation of the sympathetic nervous system through release of

relevant neurotransmitters and the block of their reuptake. The half life of amphetamines is approximately 12 times longer than cocaine (12 vs. 1 hour). Cocaine is unique in its local anesthetic effects, although it is rarely, if ever, still used for this purpose.[28]

Maternal and Fetal Effects

Both cocaine and amphetamines can produce pathologic multi-organ sympathetic stimulation resulting in myocardial ischemic, cardiac arrest, and stroke.[28] Drug-induced hypertension can mimic severe preeclampsia.[33] Maternal cocaine use has decreased from 0.4% in 2014 to unmeasurably low levels, according to the 2015 National Survey on Drug Use and Health.[1] Fetal effects of antepartum use of these stimulants are associated with placental abruption, preterm delivery, and the need for urgent cesarean delivery.[34-36] Initial concern for congenital birth defects has not been corroborated in the literature. Associations between prenatal methamphetamine exposure and childhood behavioral problems are thought to be highly associated with exposure to early adversity.[37]

Anesthetic Implications

Neuraxial analgesia or anesthesia has several advantages in parturients who have consumed stimulants. Advantages include decreasing circulating catecholamines, addressing pain management in a population where changes in μ and κ opioid receptors and altered endorphin levels may increase pain, and providing an in situ epidural catheter for conversion to surgical anesthesia in this high risk population. The thrombocytopenia initially associated with cocaine use has not been confirmed in follow up studies.[38] Challenges include potential for hemodynamic instability. Although refractory hypotension in a long-time amphetamine user has been reported, use of IV fluids and, if needed, direct-acting vasopressors are typically successful.[29,38,39]

Tips and Pearls:

- If hypotension, consider direct-acting rather than indirect acting vasopressor (e.g. phenylephrine).
- Avoid selective β-blockers leaving unopposed α blockade (i.e. choose labetalol rather than propranolol)
- Cocaine could compete for available plasma cholinesterase
- For General Anesthesia:
  - Induction:
    - Airway
      - Rotten teeth (“meth mouth”)
      - Nasal septal defects
      - Airway burns
      - Delayed gastric emptying
    - Avoid ketamine
    - Blunt hemodynamic response:
      - If hypertension, consider nitrates
  - Maintenance:
    - Changes in μ and κ opioid receptors and altered endorphin levels may increase pain
    - Acute ingestion increases MAC according to animal studies
    - Chronic ingestion decreases MAC
    - Monitor for hyperthermia

Summary

In summary, substance use disorder and the associated excessive use of opioids, alcohol, and stimulants during pregnancy can place both the parturient and the fetus at risk for adverse effects. The provision of safe and effective maternal and fetal care is facilitated by a non-judgmental culture of trust, and an understanding of the physiologic effects of the ingested substances. Whenever possible, an early anesthesia consult can facilitate planning. Opioid substitution therapy should be continued in the background to satisfy a parturient’s chronic needs, with additional acute pain management tailored to the delivery plan. In most instances, neuraxial anesthesia is the technique of choice for labor analgesia and cesarean delivery anesthesia if not otherwise contraindicated or ill-advised. If a parturient suffers from opioid use disorder or takes opioids chronically, then she is not a candidate for the mixed agonist-antagonist opioid medications frequently used for systemic labor pain management. If she has persistent labor pain despite labor epidural analgesia, then she has a dysfunctional catheter unless proven otherwise.

Working together as a multidisciplinary team with the patient can maximize patient safety, pain management and satisfaction.

Table 1: Intrapartum Buprenorphine Management Options

Options	Pro	Con
Opioid Replacement (prior to admission)	↑↑ μ receptor availability for analgesic opioids	Logistical challenge; Withdrawal Risk
Stop Dose (on admission)	↑ μ receptor availability for analgesic opioids	Risk of withdrawal; ↑opioid requirements
Usual Dose	Continuity	↑↑opioid requirements
Divided Doses	↑ analgesia	May miss doses

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Perioperative Surgical Home: Management of Diabetes and Hyperglycemia

Basem B. Abdelmalak, MD **Cleveland, Ohio**

Introduction:
Creation of evidence-based protocols for disease management preoperatively is a major component of the Perioperative Surgical Home (PSH) model proposed by the American Society of Anesthesiologists (ASA). And I would add that in the case of diabetes mellitus (DM) and/or hyperglycemia management, these protocols ought to span the intra, and post-operative phases as well. Protocols that are detailed enough to decrease variability in the overall care, however flexible enough to allow for physician judgement that is a hallmark characteristic of personalized care since one size will never fit all.[1]
The perioperative period has not received the same scrutiny in glucose control trials as in other settings, the ICU for example. However, decisions still have to be made daily to determine a safe care plan for the very same patients as they go through the perioperative experience. This review will outline a practical and comprehensive plan for perioperative glycemic management based on the available evidence, and when evidence is lacking, expert opinions, and consensus statements will be utilized. Topics discussed include: the prevalence of pre-operative hyperglycemia and the decision making process for proceeding with or delaying surgery, intraoperative hyperglycemic surgical stress response and the added effect of perioperative steroid, risks associated with hyper and hypoglycemia, a recommended target for perioperative glucose concentration, principles and strategies for safe intraoperative insulin dosing, postoperative glycemic management and a proposed algorithm for managing diabetic patients on continuous subcutaneous insulin pump therapy perioperatively.

The Prevalence of Preoperative Hyperglycemia and Undiagnosed Diabetes:
Diabetes mellitus (DM**)** affects 8.3% of the US population.**[2]** Fifty percent of diabetics will require surgery during their lifetime. A third to half of patients with type 2 DM do not know they are diabetic at the time of surgery.**[3]** Abdelmalak et al, retrospectively reviewed the records of 35,000 noncardiac surgery patients and found that 21% of the patients without a diagnosis of diabetes are hyperglycemic and more than half of those have undiagnosed diabetes.[4] Similar findings have been reported by Hatzakorzian and colleagues who prospectively studied 500 noncardiac surgery patients.[5] Among the nondiabetics, patients who are older, male,[4,5] with higher body mass index (BMI), and higher ASA Physical Status ,[4] are more likely to have hyperglycemia.

In early 2012, The Endocrine Society published their Clinical Practice Guidelines recommending blood glucose (BG) testing in all patients on admission to the hospital (including admissions for surgery) regardless of their diabetic status and further monitoring of admitted nondiabetics with BG > 140 mg/dL for 24-48 hours with appropriate therapeutic intervention. They also recommend HbA1c testing for inpatient nondiabetics whose BG concentration is >140 mg/dL, and all diabetics if it has not been done in the prior 2-3 month period.[6] These recommendations are on the basis of high prevalence of inpatient hyperglycemia, its associated poor outcomes and the opportunity to diagnose diabetes.[6] Anesthesiologists have been known for their leadership and focus on patients' safety. Perhaps this can be one area where we can add to patient care as a part of the PSH initiatives, by identifying hyperglycemic patients who are not diagnosed with diabetes and those with uncontrolled diabetes. Identifying the undiagnosed diabetics and directing them to the appropriate care has the potential to impact these patients' overall life-long well-being, beyond the perioperative period. The burden and complications of type 2 diabetes might well be reduced if it is diagnosed and treated early.[7,8]

Pre-operative HbA1c and Surgical Outcomes:
HbA1c is accepted as a marker for chronic glycemia in the few months preceding the time of measurement. Pre-operative HbA1c <7 in diabetic patients undergoing noncardiac surgery was found to be associated with a lower rate of infectious complications. [9,10] Bishop and co-workers have linked HbA1c >11.5 to surgical site infections,[11] but Wilson and co-workers have refuted that notion.[12]

Pre-op Hyperglycemia and Surgical Outcomes:
Retrospective data support the notion that pre-operative hyperglycemia is harmful in the perioperative setting. A case-control study examined pre-operative blood glucose levels and mortality in noncardiac, nonvascular surgery

patients and found that pre-operative BG levels > 200 mg/dL were associated with a 2-fold increased risk in overall mortality and a 4-fold increased cardiovascular mortality risk.[13]

Another study in patients undergoing total joint replacement showed a direct relationship between glucose concentration and the risk of pulmonary embolism (PE) with up to a 4-fold increased risk with pre-operative levels > 200 mg/dL.[14] In cardiac surgery patients, pre-operative BG > 110 mg/dL has been associated with a longer hospital stay and increased mortality.[15] Abdelmalak, et al, reviewed the records of 62,000 relatively high risk patients who underwent elective noncardiac surgery. One-year mortality – but not composite outcome of in-hospital morbidity including cardiopulmonary and infectious complications, was independently associated with pre-operative BG concentration.[16] Additionally, hyperglycemia is associated with increased production and/or impaired scavenging of reactive oxygen species,[17] polymorphonuclear neutrophil dysfunction,[18] and decreased intracellular killing.[19,20] It is thus unsurprising that poor wound healing and increased infection risk are blamed on hyperglycemia.[21]

Now, that the association of hyperglycemia with poor outcomes has been established, the question then arises, should we delay elective surgery for any identified hyperglycemia?

Delaying Surgery for Pre-operative Hyperglycemia:

Unfortunately current data offer no concrete guidance on whether an elective procedure should be delayed in light of a given level of hyperglycemia or HbA1c.[22] Moreover, when joint arthroplasty was delayed for HbA1c >7%, only 40 percent of the delayed patients were able to achieve such a target within a time range of 7-1043 days![23]

Furthermore, if the surgery gets delayed, there is no reliable data to support that if a specific "optimal target" glucose concentration and/or HbA1c are achieved and maintained for a given "optimal duration" of time pre-operatively, that it would in fact result in improvement in surgical outcomes.

Patients scheduled for surgery (plus family and loved ones) have already re-planned their lives, and took time away from work to be available for this surgery and psychologically prepared for it. Cancelling their surgery would constitute a major inconvenience with potential financial implications to the patient/family and the hospital to say the least. Therefore, the decision should be an individualized one, depending on the surgery, patient characteristics including chronic glycemic state, clinician's experience with glucose management, etc.. Thus, many clinicians do not end up delaying elective surgery for mild to moderate hyperglycemia but rather treat it, and the associated osmotic diuresis induced hypovolemia. On the other hand, many believe that it might be prudent to delay elective surgery when faced with glucose concentrations >350 mg/dL and /or any concentration associated with diabetic ketoacidosis (DKA) and/or hyperosmolar state;[24,25] DKA can easily be diagnosed based on the clinical presentation and when certain simple laboratory criteria are met; the triad of Hyperglycemia > 250 mg/dL, acidosis (arterial pH <7.3, serum bicarb < 18 mEq/l, and anion gap of >10) and ketonemia, urine and serum ketones are positive.[26] To avoid hyper and hypoglycemia pre-operatively in patients diagnosed with diabetes and treated with oral hypoglycemics and/or insulin, several plans have been recommended for scheduling their meds and doses pre-operatively. Table 1, presents one of these popular algorithms that is currently being used at the author's institution.

Diabetics Vs. nondiabetics, who should we monitor, and who should we treat?:

Abdelmalak and colleagues have shown that patients without a diagnosis of diabetes and with pre-operative hyperglycemia had higher one-year mortality than patients with diabetes with the same level of pre-operative hyperglycemia. Patients with diagnosed diabetes and pre-operative glucose concentrations in the lower euglycemic range had higher one-year mortality

Table 1

(Below regimens & doses can be adjusted on clinical judgment & individual patient basis)

Diabetic Medication:	Day Prior To Surgery	Day of Surgery
Oral Hypoglycemic	Continue same dose	Hold all on the Day of Surgery
Noninsulin injectables	Pt should take normal prescribed dose the night prior to surgery.	Hold all on the Day of Surgery
Insulin pump	Follow Insulin Pump Protocol	Follow Insulin Pump Protocol
Long Acting Basal Insulin (Levemir, Lantus, NPH)	Pt should take normal prescribed dose the night prior to surgery.	Pt should take half of the prescribed dose the morning of surgery.
Mixed Insulin (combination of long and short acting ie: 70/30 or 75/25)	Pt should take normal prescribed dose the night prior to surgery.	Pt is to check FBG, if >200mg/dL, pt is to take half the normal prescribed dose. If <200mg/dL no insulin is to be taken.

than patients without diabetes with the same levels of pre-operative euglycemia.[16] In the GLUCO-CABG trial controlling postoperative glucose to 100-140 vs. 141-180 mg/dL resulted in reduction in postoperative complication among patients without diabetes and not in those with diabetes.[27] Such findings highlight the complex relationship between glucose metabolism and outcomes and corroborates with the evidence from the ICU as well. Hyperglycaemia upon admission to the ICU has been shown to be an independent risk factor for in-hospital mortality only in patients without diabetes.[28] By the same token, Krinsley and colleagues showed that diabetics had better outcomes at higher targets than nondiabetics in the ICU.[29]

Collectively, both diabetics and nondiabetics, should be monitored and treated, and emerging evidence suggests that treating hyperglycemia may be more beneficial for nondiabetics compared to diabetics.

Hyperglycemic surgical stress response:

Major surgical procedure ⇨ release of catecholamines, glucagon, cortisol, and growth hormone ⇨ insulin resistance, glycogenolysis, gluconeogenesis ⇨ hyperglycemia.[30] Abdelmalak et al described the magnitude of intraoperative hyperglycemic response to surgical stress during major noncardiac surgery that is inversely proportional to the pre-operative glucose concentration, and the intraoperative pattern of that response in patients with and without diabetes diagnosis (Figure 1-A).[31] As noted, all patients had a sizable intraoperative hyperglycemic response, albeit those who did not have the diagnosis of diabetes had a more pronounced steep rise compared to those diagnosed with diabetes. Most of that rise was from incision to the mid surgery time point.

Steroid Induced Intraoperative Hyperglycemia:

Abdelmalak, et al,[31] have also described the hyperglycemic effects of a small dose of steroids (8 mg of dexamethasone IV) on glucose concentrations in patients with and without diabetes (Figure 1-B). Surprisingly, patients with diabetes who received steroids, compared to those who received placebo, did not have significantly different glucose concentrations. However, those without diabetes who received dexamethasone showed a small increase (approximately 30 mg/dL) compared to those who received placebo.

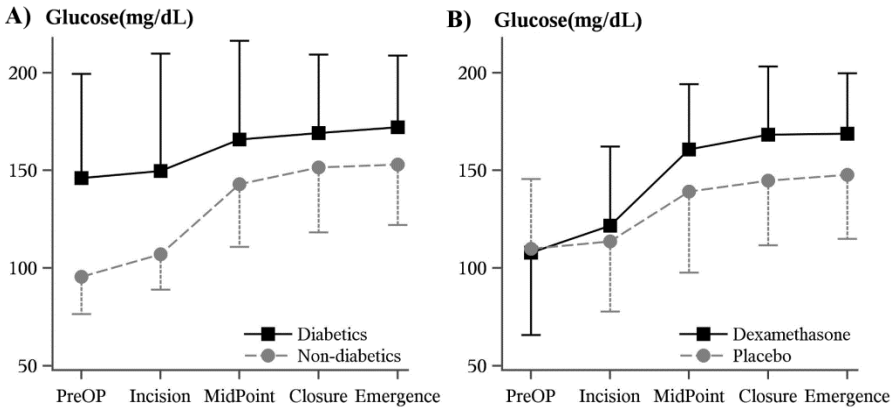

Fig. 1: Pattern of intraoperative hyperglycemic stress response over time in diabetics and nondiabetics (A), and the added effects of 8 mg of IV dexamethasone given pre-operatively in all patients (B).[28] [Reprinted with permission from Abdelmalak BB, Bonilla AM, Yang D, Chowdary HT, Gottlieb A, Lyden SP, Sessler DI: The hyperglycemic response to major noncardiac surgery and the added effect of steroid administration in patients with and without diabetes. Anesth Analg 2013; 116: 1116-22].

On the other hand, Murphy et al, found no significant increase in glucose concentrations in the first 24 hours after surgery in nondiabetics who received either 4 or 8 mg of dexamethasone perioperatively. [32]. Thus, one may not need to worry much about the long claimed hyperglycemic effect of PONV prophylaxis doses of dexamethasone neither in diabetics nor in nondiabetics.

Other factors may contribute to intraoperative hyperglycemia, such as infusing dextrose containing IV fluids, hypothermia, and dextrose containing cardioplegia solutions in cardiac surgery. Thus, whatever methodology or algorithm one would use intraoperatively to manage hyperglycemia, ought to be a dynamic one, i.e. adjusts to the

above mentioned factors that may impact the intraoperative glucose concentration such as the one the author utilized in a prior study,[33] and currently uses a modified version of the same.[34] (Figure 2)

Intraoperative Glycemic Management:
Intraoperative management is aimed at treating hyperglycemia, and avoiding hypoglycemia. Prevention and treatment of hyperglycemia has been shown to improve outcomes, on the other hand, tight glucose control did not. In the ICU, a retrospective study by Krinsley et al showed that insulin treatment reduced mortality, prevented lethal sepsis, reduced severe infections and multi-organ failure, and protected the central and the peripheral nervous systems.[35] In a landmark paper, Van den Berghe and colleagues showed in a prospective randomized trial that intensive insulin therapy to maintain blood glucose at or below 110 mg/dL substantially improved ICU outcomes.[36] However, a more recent trial aimed at treating hyperglycemia targeting tight glycemic control (80-110 mg/dL) did not improve outcomes.[37] Furthermore, some investigations of intensive insulin therapy in the ICU reported a higher risk of hypoglycemia without a mortality benefit.[37-40]

In the perioperative period, a prospective study of 2,467 cardiac surgical patients revealed that continuous IV insulin infusion reduced the incidence of deep sternal wound infection in diabetic patients. Subsequently, the same authors found that continuous insulin infusion reduced mortality in patients with diabetes undergoing coronary artery bypass grafting.[41,42] However, a single center randomized trial by Gandhi et al where they randomly assigned 400 cardiac surgery patients to tight glycemic control (80-100 mg/dL) intraoperatively or usual care (no insulin during surgery unless BG levels were > 200 mg/ dL) did not show any difference in outcomes between the two groups.[43] Carvalho and colleagues studied the effects of a glucose, insulin, potassium (GIK) regimen while maintaining normoglycemia (the so-called GIN therapy) during cardiac surgery and showed that such a strategy provided more cardioprotection than GIK without maintaining normoglycemia.[44] The hyperinsulinemic clamp technique while appears to be promising, it remains under investigation.[45]

Duncan and colleagues, in their retrospective study, reported that in cardiac surgery, intraoperative glucose concentrations > 200, and < 140 mg/dL were associated with increased morbidity and mortality, and 141-170 mg/dL was a safer range.[46] In a randomized trial, Abdelmalak et al reported that intraoperative tight glucose control did not

PERIOPERATIVE GLUCOSE CONTROL PROTOCOL

The target range for blood glucose is 140-180 mg/dl.

Discontinue all previous orders for insulin and oral glucose lowering agents
Must use infusion pump and run with maintenance fluid
Insulin concentration will be 1 unit of regular insulin/ml of normal saline
- Please prime the tubing with 25-50 ml of the insulin solution

Blood glucose monitoring
- Check BG in 30 minutes after starting the insulin infusion or after a bolus or change of infusion rate. BG may be checked at longer intervals (e.g., 60 min) if there was no intervention in the term of an insulin bolus or a change of infusion rate and if the concentration has been stable for two readings.
- BG may be checked via ABG or bedside monitor. However, sampling site and lab analysis should remain consistent.
  - Verify BG results using an alternate method (e.g. fingerstick) for:
    - Variations in BG lab results ≥ 100mg/dl on consecutive blood draws
    - Suspicion of false lab results or contaminated specimen
    - BG results reading "Hi" or "Low" on the accu-check meter

Calculation of Insulin infusion change
- If DECREASING RATE by 50%: New rate= Current rate 0.5
- If DECREASING RATE by 25%: New rate= Current rate 0.75
- If INCREASING RATE by 50%: New rate= Current rate 1.5
- If INCREASING RATE by 25%: New rate= Current rate 1.25

Initiation of Insulin Infusion†

Blood Glucose (mg/dL)	*Bolus – (IV)*	*Start Infusion at:*
181-200	2 units	2 units/hour, recheck in ½ hour
201-250	3 units	3 units/hour, recheck in ½ hour
251-300	4 units	4 units/hour, recheck in ½ hour
300-350	6 units	6 units/hour, recheck in ½ hour
>350	7 units	8 units/hour, recheck in ½ hour

How To Adjust Insulin Infusions

Please use the re-check glucose concentration (½ hour after the initial bolus and infusion as above) to identify the corresponding row in the table below. Choose the recommended next step from the column that corresponds with the amount of change in glucose concentrations from the prior value.

Blood Glucose (mg/dL)	Decreasing Blood Glucose (↓ by more than 30 mg/dL)	Stable Blood Glucose (No more than 30 mg/dL ↓ or ↑)	Increasing Blood Glucose (↑ by more than 30 mg/dL)	Re-check in
<70	Hold infusion, give 12.5-25 ml dextrose 50%. Notify staff anesthesiologist	Hold infusion, give 12.5-25 ml dextrose 50%. Notify staff anesthesiologist	Hold infusion, give 12.5-25 ml dextrose 50%. Notify staff anesthesiologist	Immediately
71-140	Stop infusion	Stop infusion	Decrease the infusion by 50%	½ hour
141 – 180	Stop infusion	Continue same rate	Increase rate by 25%* ***Max. increase = 10 units/hr**	½ hour
181-200	Decrease rate by 25%	Bolus 2 units I.V. and increase rate by 25%* ***Max. increase = 10 units/hr**	Bolus 2 units I.V. and increase rate by 25%* ***Max. increase = 10 units/hr**	½ hour
201-250	Continue same rate	Bolus 3 units I.V. and increase rate by 50%* ***Max increase = 10 units/hr**	Bolus 3 units I. V. and increase rate by 50%* ***Max. increase = 10 units/hr**	½ hour
251-300	Bolus 3 units I.V. and continuous same rate	Bolus 3 units I. V. and increase rate by 50% ***Max. increase = 10 units/hr**	Bolus 4 units I.V. and increase rate by 50% ***Max. increase = 10 units/hr**	½ hour
301-350	Bolus 4 units I.V. and continue same rate	Bolus 4 units I.V. and increase rate by 50% ***Max. increase = 10 units/hr**	Bolus 5 units I. V. and increase rate by 50% ***Max. increase = 10 units/hr**	½ hour
351-400	Bolus 5 units I. V. and continuous same rate	Bolus 5 units I. V. and increase rate by 50% ***Max. increase = 10 units/hr**	Bolus 7 units I. V. and increase rate by 50% ***Max. increase = 10 units/hr**	½ hour
>400	Bolus 7units I.V. and continuous same rate Notify staff anesthesiologist	Bolus 7 units I. V. and increase rate by 50% ***Max. increase = 10 units/hr** Notify staff anesthesiologist	Bolus 10 units I. V. and increase rate by 50% ***Max. increase = 10 units/hr** Notify staff anesthesiologist	½ hour

Fig. 2 An example of and intraoperative insulin infusion titration algorithm targeting moderate glucose control 140-180 mg/dL. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2017. All rights reserved.

improve surgical outcomes in patients undergoing major noncardiac surgery.[47] Finfer and colleagues in their randomized trial in ICU patients, showed that a glucose target of <180 mg/dL was associated with improved outcomes compared to a tight target of 81-108.[37] ***Thus, current recommendations from different national societies (citing only a sample here) favor rather moderate targets in the range of 140-180 mg/d,.[6,37,48] vs. tight or more liberal targets.***

The advances in technology may help clinicians in paying more attention to glycemic management. The use of a novel intraoperative audiovisual alert system has resulted in an increase in initiation of insulin treatment and in re-checking glucose value afterwards.[49]

Route of insulin administration perioperatively:
While the subcutaneous route is being viewed as a safe route by many clinicians and may have a role in managing moderate hyperglycemia in ambulatory surgery patients,[50], it has the disadvantages of a very slow onset compared to IV as well as longer duration of action, that makes titratability a challenging task to say the least, and would not allow for timely management of dangerously severe hyperglycemia and thus the risk of "stacking" doses that may eventually result in hypoglycemia.[50] [22] In addition, the change in the subcutaneous circulation due to fluid shifts and change of temperature from exposure to cold operating rooms, to forced air skin warming devices application make SQ absorption variable and not very reliable.[30]

Another important point to discuss is that the SQ route is appropriate for postoperative management, an insulin regimen in the form of a long acting basal, plus boluses [preprandial (if feeding is started), and to treat episodic hyperglycemia] is preferred over the traditional sliding scale of insulin (SSI).[6] SSI is based on repeated responses to hyperglycemia resulting in glucose variability that has been found to correlate with poor outcomes in various populations. Glycemic variability is an independent risk factor for mortality in the ICU.[51,52] and in septic patients.[53] This may explain why the use of insulin infusion with boluses, presumably with better glucose management and low variability, results in less all-cause mortality and fewer poor cardiac outcomes than intermittent IV bolusing of short-acting insulin despite the same glycemic control target.[54]

Thus the intravenous infusion with intermittent boluses approach is recommended whenever feasible especially in long surgeries. The intravenous algorithm used will need to be a dynamic one adjusting for variability in individual patient's response (insulin sensitivity), the stage of surgery and other factors affecting intraoperative glucose concentrations (see above discussion on hyperglycemic surgical stress response, and the added effects of steroid administration), such algorithm should also dictate when glucose measurements should be performed, and an intervention plan for detected hypoglycemia. An example of such protocol is presented in Figure 2.[34] ***In all cases, no one algorithm will replace physician's judgement based on an ongoing assessment of the changing clinical status of the patient which is essential in making decisions in dosing and titrating insulin perioperatively***.

Intraoperative Insulin Sensitivity:
Some insulin dosing algorithms adjust for patient-related factors such as weight,[6] and diabetic status,[55,56] while others do not.[37-39] There is no consensus about which baseline factors should be included, although insulin sensitivity has been related to various factors in non-operative settings. In noncardiac surgery, it appears as if the diabetic status, and body weight contribute little if any (contrary to the common belief) to the response to a given insulin bolus.[57] Regardless of the insulin sensitivity, the use of a dynamic insulin algorithm like the one presented (Figure 2) in which insulin dosing does not depend only on the measured glucose concentration but also on the delta change from the prior measurement, should account for differences in insulin sensitivity resulting from identified or unidentified factors as well as other external factors influencing glucose concentrations like the administration of glucose containing solutions, and glucose containing cardioplegic solutions in cardiac surgery.

Safety of Glycemic Control:
While hyperglycemia is detrimental, hypoglycemia is not without risk and even more dangerous than hyperglycemia. Hypoglycemia per se can increase mortality and morbidity and results in increased neurological damage. Severe hypoglycemia was shown to result in somnolence, unconsciousness, seizures,[58] and — when sustained sufficiently — irreversible neurologic sequelae and/or death.[59] Not only severe but also moderate hypoglycemia was found to be associated with mortality in ICU patients.[60] Clinicians understandably are concerned about tightly controlling glucose perioperatively due to the high incidence of hypoglycemia in association with intensive glucose control;[37-39,61] whose symptoms are masked by general anesthesia and sedation,[62] and no proven benefit.[37-39] Even when we were able to tightly control glucose without inducing severe hypoglycemia in noncardiac

surgery patients,[33] no benefit was shown.[47] Thus a moderate control target has been proposed especially since they have been proven beneficial at least in the ICU population.[37]

Management of diabetic patients with insulin pumps:
Although evidence is lacking when it comes to managing patients using insulin pumps perioperatively, several individual or institutional care paths have been developed.[63,64]

Figure 3 outlines a proposed plan for perioperative management of insulin pump patients that is being utilized currently at the author's institution. The reader is referred to reference number 34 for a comprehensive discussion of this topic, and rationale for every proposed step in this algorithm.[34]

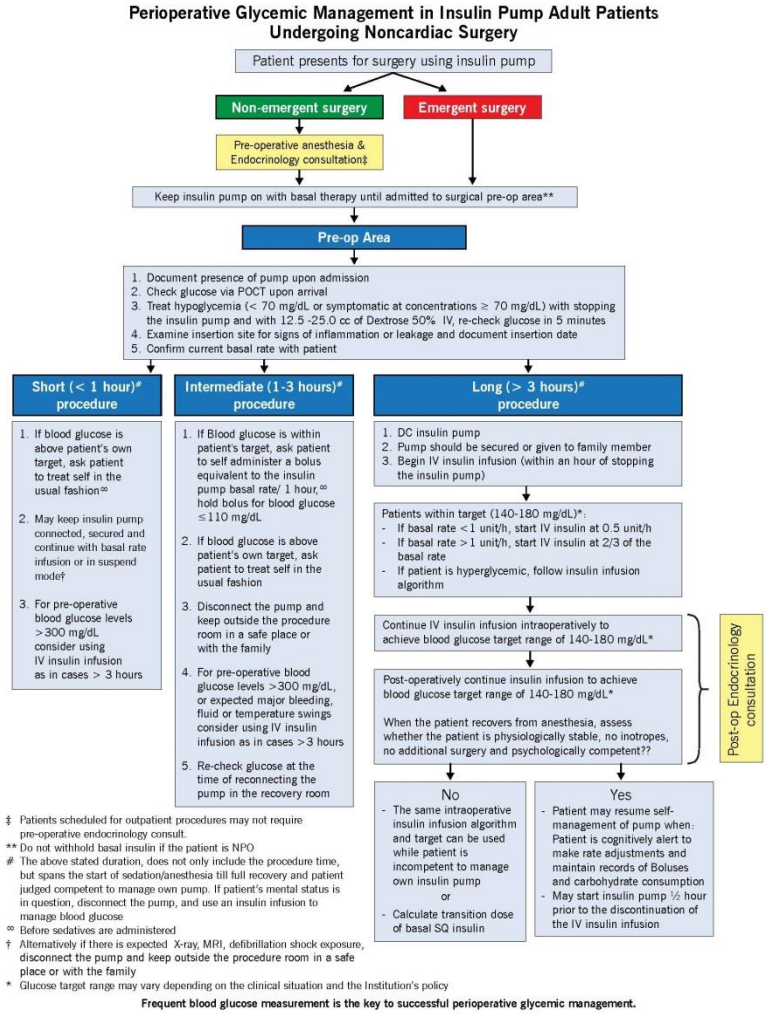

Fig. 3: Perioperative Glycemic Management in Insulin Pump Patients Undergoing Noncardiac Surgery. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2017. All rights reserved.

Postoperative Glycemic Management:
In noncardiac surgery patients, Ramos et al,[65] in their retrospective study of 995 patients, concluded that postoperative hyperglycemia increased the risk of postoperative infections irrespective of diabetic status. Frisch and colleagues did a retrospective study of over 3000 noncardiac surgery patients. The results were that patients with hyperglycemia had worse outcomes (i.e. postoperative infections, acute renal failure, acute myocardial infarction, and 30-day mortality), as well as longer ICU and hospital stays. In both cardiac and noncardiac surgery,

postoperative hyperglycemia increased the infectious complication risk.[66] Thus, avoiding hyperglycemia is recommended postoperatively and moderate targets are preferred.[6] In doing so, the so called basal bolus regimen has been found to be superior to the SSI approach.[67] And more recently, both basal bolus and basal plus regimens have both been more effective compared to SSI.[68] It is thought that compared to SSI, the latter two techniques provide less glycemic variability which has been linked to poor outcomes as discussed above.

Glucose Measurement:
The central laboratory's measurement of blood glucose remains the gold standard; however, it is costly and takes time. Point of care testing (POCT) devices while they tend to overestimate the actual glucose concentration value,[69] they are cheap, readily available, and fast; providing a good resource for implementing effective glucose management strategy.[6] The advantage of the continuous interstitial fluid glucometer is that it is convenient and it provides frequent readings; however, the drawback is that it has a lag period between blood and tissue glucose concentrations. When one methodology is used (such as POCT), the sampling site and the methodology should remain consistent throughout the procedure.

Emerging Technology and Advances:
An inhalational insulin has been approved by FDA, and under development is a noninvasive app based glucometer (GlucoWise™, Medwise, London, UK). Their roles in the perioperative period is yet to be studied and understood.

Summary: An alarming proportion of our surgical patients are hyperglycemic and many are undiagnosed diabetics. Hyperglycemic surgical stress response is real and is not linear throughout surgery. Perioperative steroids induce a small hyperglycemic response if any. Close monitoring of blood glucose levels intraoperatively is of prime importance especially if treatment has been initiated. Signs and symptoms of hypo and hyperglycemia are for the most part masked by general anesthesia. Consequences of untreated hypoglycemia are grave. Current evidence supports IV insulin infusion with boluses for BG management intraoperatively. Insulin pump patients should be managed very carefully according to a standard protocol.

A perioperative glucose management strategy should be implemented to some degree for hyperglycemic patients. Intra-operative tight glucose control is not beneficial in cardiac or in noncardiac surgery. It is pre-mature to mandate certain glucose values in light of insufficient evidence. Current recommendations call for moderate control.

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Lung Isolation: Clilnical Challenges and Strategies for Success

Jerome M. Klafta, MD **Chicago, Illinois**

Success in the context of one-lung anesthesia means that lung collapse is both complete *and* well tolerated by the patient. Although the concept is simple, a number of clinical details frequently make the difference between success and failure. Lung isolation (functional lung separation) allows us to ventilate one lung independent of the other (airtight seal) or to restrict passage of blood or fluids (watertight seal) from one lung to another. One-lung anesthesia requires *not only* functional lung separation *but also* adequate one-lung ventilation and oxygenation. Figure 1 depicts the three clinical end points integral to one-lung anesthesia:

- Optimal position of double-lumen tube (DLT) or bronchial blocker (BB)
- Functional lung separation
- Adequate one-lung ventilation and oxygenation

Various overlapping subsets of these conditions can and do occur. For example, adequate position of the DLT or BB does not ensure functional lung separation (condition A), and adequate one-lung ventilation can sometimes be achieved with *suboptimal* DLT position (condition C). Table 1 lists examples of causes and solutions for each clinical condition in Figure 1. By identifying the exact nature of the difficulties, the anesthesiologist can implement appropriate therapy without wasting time on maneuvers (DLT repositioning, cuff volume manipu-lations, or ventilation changes) that are not part of the problem.

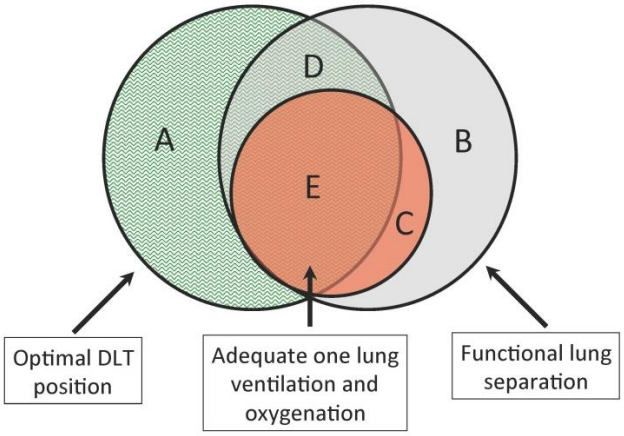

Figure 1. Overlap of clinical end points in one-lung anesthesia. *A, B, C, D,* and *E* represent different clinical end points as described in Table 1.

Design Characteristics of Double-Lumen Tubes and Bronchial Blockers
Common adult DLT sizes are 35, 37, 39, and 41 French (F). Some manufacturers also provide 26, 28, and 32F sizes. The particular dimensions and design characteristics vary somewhat between manufacturers (Rüsch, Portex, Sheridan, Mallinckrodt, and Fuji Systems). The resting bronchial cuff volume (defined as the smallest cuff volume beyond which a 0.5 cc increase results in more than a 10 torr increase in cuff pressure) can differ between sizes (35F = 3.7 cc; 41F = 2.0 cc).[1] Inflation of the bronchial cuff beyond its resting volume (or even less than its resting volume if fitted tightly inside a bronchus) may result in dangerously high intracuff pressures and should be avoided.[1,2]

Table 1. Clinical Conditions during One-Lung Anesthesia

Area [a]	*Example Situation*	*Typical Solution*
A	No airtight cuff seal – lungs not separated	More air in cuff or larger DLT
B	Left DLT inserted too far, occluding left upper lobe orifice	Position DLT optimally
C	Right DLT cuff occluding right upper lobe orifice	Position DLT optimally
D	• Hypoxemia • Obstruction of the ventilating lumen of the DLT	• 100% oxygen/CPAP/PEEP/TLV • Consider alternative lung separation technique
E	No problem!	

[a] See Figure 1.

CPAP, continuous positive airway pressure; *DLT*, double-lumen tube; *PEEP*, positive end expiratory pressure; *TLV*, two-lung ventilation.

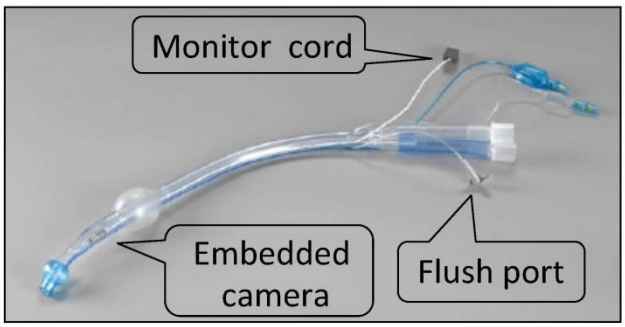

Figure 2. The VivaSight™-DL double-lumen tube (ETView, Misgav, Israel). A high-resolution camera is embedded below the tracheal cuff. Next to the balloons of the bronchial and tracheal cuffs, a white cable connects the camera to an external monitor. An extra side-port is available for flushing the camera lens with saline.

A new left-sided DLT with integrated camera, the VivaSight™-DL (Figure 2), allows for continuous visualization of the tracheal carina, once correctly placed.[3] In a study comparing this device with conventional DLTs placed blindly, intubation time was faster (63 *vs.* 97 sec) and correct initial positioning was facilitated.[4] In another study, loss of video image quality because of secretions occurred in 30% of patients despite use of the integrated flushing mechanism.[5] It appears that this device can provide helpful continuous visual monitoring of DLT position but is unlikely to supplant use of the fiberoptic bronchoscope.

The Univent Torque Control Blocker (Figure 3) is shaped like a standard single-lumen tube (SLT) but has two lumens: one housing a retractable BB and the other used for gas exchange. Typical cuff inflation volume of the blocker balloon is 5 to 6 cc.

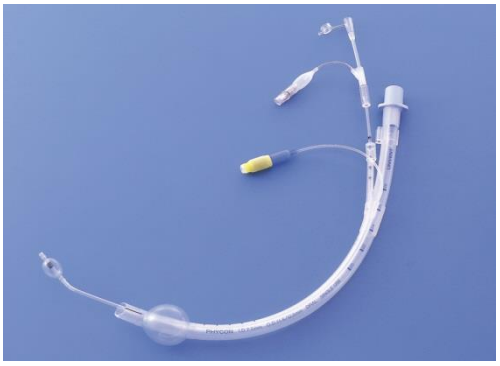

Figure 3. The TCB Univent torque control blocker (Fuji Systems, Tokyo, Japan).

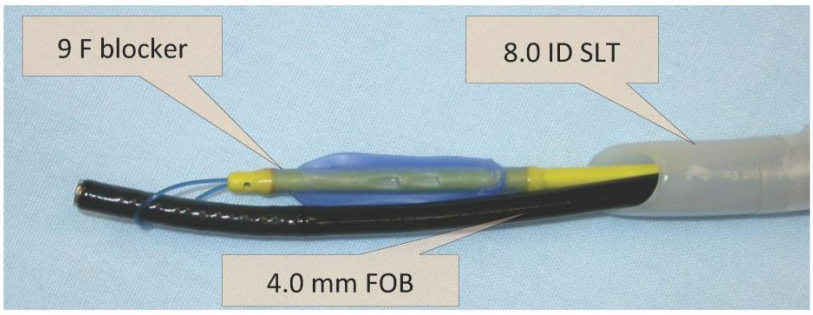

Figure 4. Coaxial use of the Arndt Endobronchial Blocker (Cook Critical Care, Bloomington, IN) illustrating the critical interdependence of the BB, SLT, and FOB sizes.

The Arndt Endobronchial Blocker (Figure 4) was the first of several additions to our current armamentarium of lung separation devices. This system minimizes some of the traditional difficulties associated with the use of Fogarty embolectomy catheters as independent BBs and with Univent tubes. A patient's lungs can be conveniently ventilated while the blocker is fiberoptically positioned through the Arndt multiport airway adapter. The guidewire loop that protrudes through the blocker's tip is used to couple the blocker to the fiberoptic bronchoscope, which can be directed fiberoptically to the desired location in the bronchial tree. The blocker's 1.4-mm lumen can be used to insufflate oxygen or suction gas from the blocked lung after the wire loop is removed. The smallest SLT for use with this blocker coaxially (≥7.5 mm ID) has a corresponding outer diameter that compares favorably with that of the typical DLTs and Univent tubes used for small adults.

Cook Critical Care has made several design modifications to the Arndt blocker since its introduction in 1999. Characteristics of available blockers are described in Table 2. A midsize 7F catheter permits the use of a larger-diameter fiberoptic bronchoscope *or* a smaller-diameter SLT for coaxial use. "Murphy eye" side holes have been introduced into the distal end of the 9F adult catheter to circumvent suctioning difficulty if the end hole abuts the bronchial mucosa, and the guidewire loop of the 9F blocker can now be reinserted if needed.

Table 2. Arndt Endobronchial Blockers

Size (F)	*Smallest SLT ID for Coaxial Use (mm)* [a]	*Length (cm)*	*Cuff Shape*	*Average Cuff Inflation Volume (cc)*
9	7.5	78	Spherical	4–8
7	6.5	65	Spherical	2–6
5	4.5	50	Spherical	0.5–2.0

[a] With 3.4 mm fiberoptic bronchoscope (data from www.cookmedical.com).
ID, inner diameter; *SLT*, single-lumen tube.

The Cohen blocker is similar to the Arndt blocker except that its distal tip is directed by way of a proximal control mechanism instead of coupling to a bronchoscope. The Uniblocker is an independent BB controlled similarly to the one integral to the Univent tube. The use of BBs in adults for routine cases[6] and for selective lobar blockade[7] has been reviewed.

The Y-shaped, dual-balloon Rüsch® EZ-Blocker™ (Figure 5) is the newest BB design. When compared with left-sided DLTs in 100 patients, an SLT plus EZ-Blocker performed similarly (intraoperative malposition, speed and quality of lung collapse, gas exchange) and took only slightly longer (25 *vs.* 13 sec) to place.[8] Importantly, the incidence of airway injury as assessed by an independent bronchoscopist was less with the EZ-Blocker, as were postoperative hoarseness and sore throat. A horizontal orientation in the supine position facilitates correct initial placement of this device.

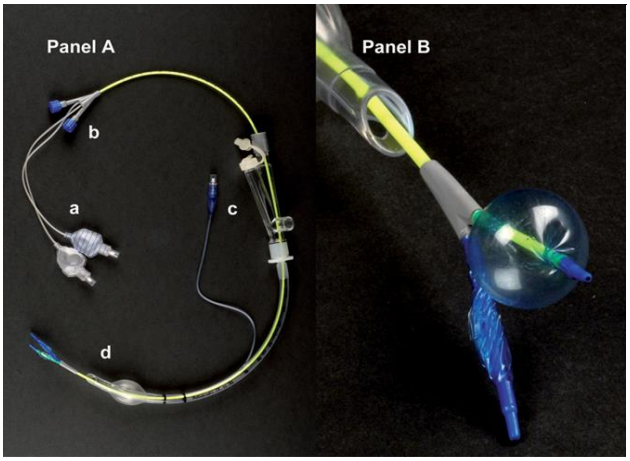

Figure 5. The Rüsch® EZ-Blocker™ (Teleflex, Morrisvil e, NC) placed through a single-lumen tube (7 mm ID). (A) An overview of the EZ-Blocker, a 7F, 75-cm, 4-lumen catheter. (B) Close-up view of the distal end. The blocker is protruding from the endotracheal tube. Photographs take n by Anja Prischmann, medical photographer, and used with permission. From Mourisse *et al.*[8]

Size Selection of Double-Lumen Tubes

Assuming that the main body of a DLT will fit through the glottic opening and the trachea, an appropriately sized DLT is the largest tube that will fit in the main bronchus with only a small air leak detectable when the cuff is deflated.[2] The presence of some air leak ensures that the tube is not tightly impacted in the bronchus. Thus, the goal is to select a DLT with an outer bronchial diameter that is 1 to 2 mm smaller than the diameter of the intubated bronchus to allow for the size of the deflated cuff.[2] Although some practitioners use 35F DLTs for *all* patients,[9] many select 41F and 39F DLTs for tall and short men, respectively, and 39F and 37 or 35F DLTs for tall and short women, respectively. There is considerable variability in the diameters of left main bronchi, however, and the relatively weak predictive value of gender and height has been repeatedly demonstrated.[2,10] Because prediction is imprecise, measurement of the left main bronchus diameter is most reliable. On chest x-ray it is discernible only 50% to 69% of the time,[2,11] but it is reliably identified on chest CT.[12] *Checking the radiograph to identify unexpectedly large or small bronchi (i.e., significant outliers) is probably most important.*

One critically important assumption is that we clinicians know the dimensions of the different sized DLTs. Russell and Strong[13] independently measured the dimensions of DLTs from four manufacturers and found marked variations, even within the same tube size for each manufacturer! (Figure 6). Thus, any effort to predict appropriate DLT size has this important limitation. Although attempting to select an appropriately sized DLT is important, it is equally important clinically to recognize when a DLT is too large (bronchial lumen will not fit in the bronchus or forms an airtight seal with no air in the cuff) or too small (requires more than ~3 cc of air in the bronchial cuff to create a seal), and adjust accordingly.

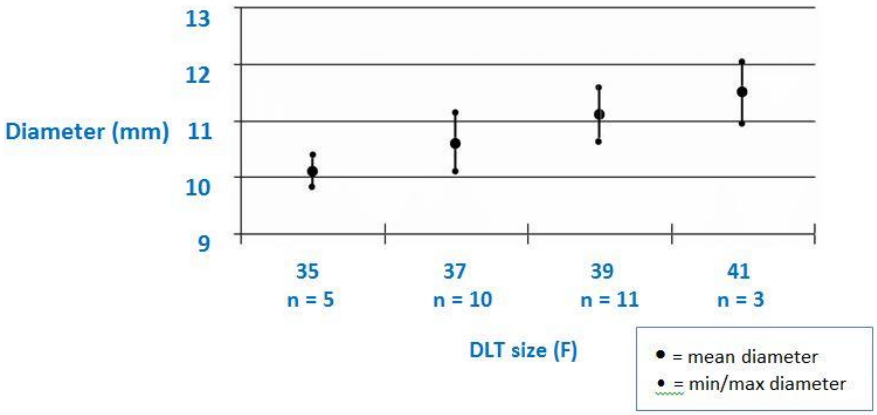

Figure 6. Variation in bronchial outside diameters of Mallinckrodt double-lumen tubes (DLT). Modified from Russell and Strong.[13] Reproduced from *Anaesthesia and Intensive Care* with the kind permission of the Australian Society of Anaesthetists.

Right-Sided Double-Lumen Tubes

The perceived or real difficulty in achieving adequate one-lung ventilation with right-sided DLTs is evidenced by the fact that they are used much less frequently than are left-sided DLTs: currently, 96% of sales of the Broncho-Cath™ (Medtronic, Minneapolis, MN) are for the left-sided device (Erich Weiss, personal communication, 2016). Use of left-sided DLTs is generally encouraged because of the greater margin of safety in positioning them, but a retrospective analysis of 691 cases demonstrated indistinguishable oxygenation, ventilation, and airway pressure performance between right- and left-sided DLTs.[14] Moreover, in the hands of *infrequent* users of DLTs, the three aforementioned performance criteria were *less favorable* with left-sided tubes.[15]

When right- and left-sided DLTs were compared for left-sided thoracic surgery in 40 patients, no right upper lobes collapsed and the difference in the time to place the tubes was clinically insignificant (3.37 *vs.* 2.08 min).[16] Although their routine use in thoracic surgery is controversial,[16,17] right-sided DLTs are indicated when a patient requires a DLT but also has an anatomical abnormality of the left main bronchus such as an exophytic or stenotic lesion or left main bronchus disruption. Regardless of the reasons for use, right main bronchial length of at least 23 mm best accommodates the bronchial cuff and facilitates successful use.[18] This length can be determined bronchoscopically or from a chest x-ray or CT. Attempts to position a right-sided DLT in patients whose right main bronchi are too short are almost certainly doomed to failure.

Fiberoptic Placement and Positioning of Double-Lumen Tubes

Precise positioning of a DLT is most reliably achieved with the benefit of a fiberoptic bronchoscope. In comparisons of fiberoptic positioning of DLTs with conventional methods, more than one-third of left DLTs were malpositioned after blind intubation and the inspection and auscultatory method.[19] In a study of 200 patients, the incidence of malposition (0.5 cm deviation from ideal position) was 39.5% with 14% of them deemed "critical."[20] Critical malpositions were those in which the left endobronchial limb allowed no clear view of the left upper or lower lobe bronchus, the right endobronchial limb allowed no clear view of the right upper lobe bronchus, or there was intratracheal dislocation of more than one-half of the endobronchial cuff. Visually unassisted placement of left DLTs may result in initial intubation of the wrong bronchus 7% to 30% of the time.[20-23]

Ovassapian described a reliable and reproducible method for placing left-sided tubes (and right-sided, with slight modification) on the first attempt.[22] The technique involves first inserting the DLT through the glottis with direct laryngoscopy, rotating it 90° leftward, and advancing it *only until* the proximal edge of the tracheal cuff is past the vocal cords. This limited advancement ensures that the tip of the bronchial lumen is supracarinal. After the tracheal cuff is inflated, ventilation through both lungs is initiated. The fiberoptic bronchoscope is then placed through the *bronchial* lumen and advanced until the carina and main bronchi are clearly identified. The posterior membranous portion of the trachea, the 5 cm left main bronchus, and the characteristic trifurcation of the right upper lobe bronchus are reliable anatomical landmarks to facilitate directional orientation. The fiberoptic bronchoscope is then

advanced into the left main bronchus to a position just proximal to the left upper and left lower lobe bronchi. After deflation of the tracheal cuff, the entire DLT is slid over the fiberoptic bronchoscope until its bronchial lumen comes into view beyond the tip of the device. Confirmation of a patent left upper and left lower lobe bronchus ensures that the DLT is not in too far. Finally, the fiberoptic bronchoscope is passed through the tracheal lumen to check for a carinal or subcarinal position of the bronchial cuff and ensure patency of the right main bronchus.

Initial passage of left-sided DLTs through the glottis can sometimes be difficult using the typical 90° counterclockwise rotation. In a recent study, 164 patients were randomly allocated to 90° or 180° left-sided DLT rotation once the tip of the bronchial lumen passed the glottis. The 180° rotation facilitated DLT passage through the glottis and reduced the incidence of postoperative sore throat (20% *vs.* 40%) and vocal cord trauma (19% *vs.* 47%). All 9 of the 84 DLTs that could not be advanced after 90° rotation were successfully placed with 180° rotation. The authors acknowledged that attention to re-rotating 90° *clockwise* in the 180° group is important, lest the posterior membranous wall of the trachea be injured.[24] Another recent study using three-dimensional chest CT reconstructions demonstrated that *the left main bronchus branches not only horizontally, but posteriorly as well, at an average of 108° to the sagittal midline*.[25] This finding was consistent with those authors' clinical experience that "over-rotating" left-sided DLTs to ~110° results in more successful placements. While intriguing, this radiological finding and its clinical correlation have not yet been demonstrated prospectively.

When 50 thoracic surgical patients with left-sided DLTs were positioned from supine to lateral, the tubes tended to move outward by an average of about 1 cm.[26] Inflation of the endobronchial cuff before lateral positioning *did not* decrease the incidence of this movement or the amount of overall distance change. Because of the tendency for carinal shift and DLT movement upward with lateral positioning, *there is an advantage to keeping the bronchial cuff 5 to 10 mm inside the left main bronchus before turning the patient laterally*. In another study, of 61 patients, the incidence of proximal repositioning was reduced significantly (43% *vs.*16%) after turning from supine to lateral when the left Broncho-Cath was initially inserted with the proximal edge of its bronchial cuff 5 mm beyond the tracheal carina.[27] Initially positioning the DLT without a headrest may minimize the displacement.[28] This same tendency toward outward movement was also recently demonstrated in cadavers.[29]

Confirming Lung Separation

Of the techniques described to achieve a minimum occlusive seal,[30-32] I routinely use the positive pressure test or bubble test depicted in Figure 7. There are a number of reasons to use a "just seal" technique to inflate the bronchial cuff of a DLT or BB

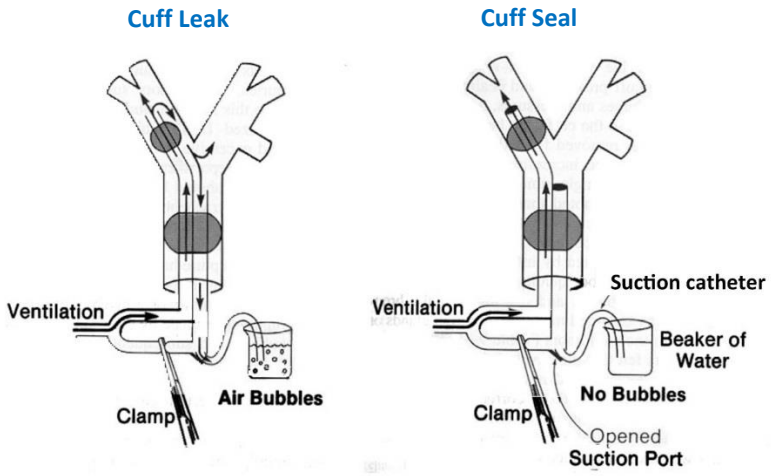

Figure 7. Air bubble method for detection of cuff seal/leak. Modified from Benumof.[30]

First, a cuff that is inflated beyond a minimum occlusive pressure may result in ischemia or even rupture of the bronchial mucosa.[31,33] Second, an overinflated bronchial cuff or BB is more likely to herniate over the tracheal carina and interfere with contralateral ventilation. Third is the ability to immediately and definitively verify lung

separation. That "moment of truth" when the thoracoscopic port is inserted or the hemithorax is opened is *thoroughly predictable*. If lung collapse is slow or incomplete, documented lung separation assures the anesthesiologist that manipulation of the DLT or BB or their cuffs will not improve the situation. Attention can be focused on other maneuvers that will improve the surgical exposure: manual compression, suction, additional time, or intra-hemithoracic CO_2 insufflation.[34]

Facilitating Lung Collapse

Once functional lung separation is confirmed and one-lung ventilation begins, collapse of the nonventilated lung occurs in two phases. The first phase is secondary to lung elastic recoil and commences with pleural opening when ambient air enters the pleural space. This phase is terminated by small airways closure. The second, slower phase is caused by absorption atelectasis.[35] This atelectasis was achieved most rapidly with DLTs using an N_2O/O_2 mixture ($FiO_2 = 40\%$), then 100% O_2, and then air/O_2 ($FiO_2 = 40\%$) because of the diffusion differences of these gases.[36,37] Moreover, lung collapse will be most rapid if lung separation is initiated at end expiration (at functional residual capacity), especially when using a BB that has a small or absent lumen.[30] The use of 50% N_2O prior to the initiation of one-lung ventilation using BBs has also been shown to facilitate lung collapse without compromising oxygenation.[38] Most recently, in a study comparing BBs with DLTs in patients with normal lung elastic recoil undergoing video-assisted thoracoscopic surgery procedures, instituting two periods of apnea (the first prior to initiating one-lung ventilation, the second coincident with opening the pleura) resulted in significantly faster and more complete lung collapse with BBs than with DLTs.[39] Despite the frequent use of suction to facilitate lung collapse, data supporting its utility are not compelling.

Comparison of Lung Isolation Techniques

Campos and Kernstine[40] prospectively compared the effectiveness of lung isolation with a left Broncho-Cath, Univent Torque Control Blocker tube, and the Arndt Endobronchial Blocker through an SLT in 64 elective right- and left-sided thoracic surgical cases. There were no statistically significant differences among the three groups in frequency of tube malpositions, number of required bronchoscopies, or overall quality of lung isolation as assessed by the surgeon (blinded to technique) once lung isolation was achieved. The Arndt blocker took slightly longer to place (3 min, 34 sec) compared to the DLT (2 min, 8 sec) or Univent (2 min, 38 sec) groups, inclusive of time to place the SLT, although 86- and 46-sec differences are hardly of clinical significance. Complete lung collapse took longer with the Arndt blocker (26 min, 2 sec) than with the DLT (17 min, 54 sec) or Univent (19 min, 28 sec), and more frequently required suction assistance.

Campos *et al*.[41] also studied the success with which the occasional thoracic anesthesiologist (<2 cases per month) correctly placed and positioned these same three devices in 66 patients with favorable airways. They found an astonishing overall failure rate of 38% with no differences among devices! When successful, placement times averaged between 6 and 9 minutes regardless of the device used. *Their observations suggested that unfamiliarity with tracheobronchial anatomy and lack of skill in fiberoptic bronchoscopy were most responsible for the difficulties.* An excellent web-based resource for self-assessment and learning of tracheobronchial anatomy is the Bronchial Anatomy Quiz and Bronchoscopy Simulator developed by Drs. Kanellakos, Dugas, Wong, and Slinger.

When a left Broncho-Cath DLT was compared to the Arndt BB for port-access cardiac surgery, more laryngoscopy attempts (2.3 *vs.* 1.1) and additional time (105 sec) to replace the DLT at the end of the case were trade-offs for slightly better right lung deflation with DLTs.[42] More recently, a comparison of three different BBs to left DLTs for left-sided surgery, all four devices provided equivalent surgical exposure at 10 and 20 minutes after pleural opening.[43] Postoperative hoarseness was prospectively found to be more common with DLTs (44%) than with BBs (17%).[44]

A 2015 meta-analysis sought to determine the efficacy and adverse effects of BBs and DLTs.[45] Of 39 RCTs published between 1996 and 2013, 13 met inclusion criteria. Overall, DLTs were quicker to place than BBs (mean difference = 51 sec) and were less likely to be incorrectly positioned (odds ratio = 2.70). However, patients managed with BBs had fewer sore throats (odds ratio = 0.39), less hoarseness (odds ratio = 0.43), and fewer airway injuries (odds ratio = 0.40) than with DLTs.[45]

Lung separation and the difficult airway

In the patient with a difficult airway who requires lung separation, the concern for providing lung separation is subordinate to securing the airway. Several options exist for achieving lung separation once an SLT has been successfully placed. BBs are especially useful in these situ-ations, particularly when a nasal intubation is required.[46] An algorithm for airway management options is presented in Figure 8.

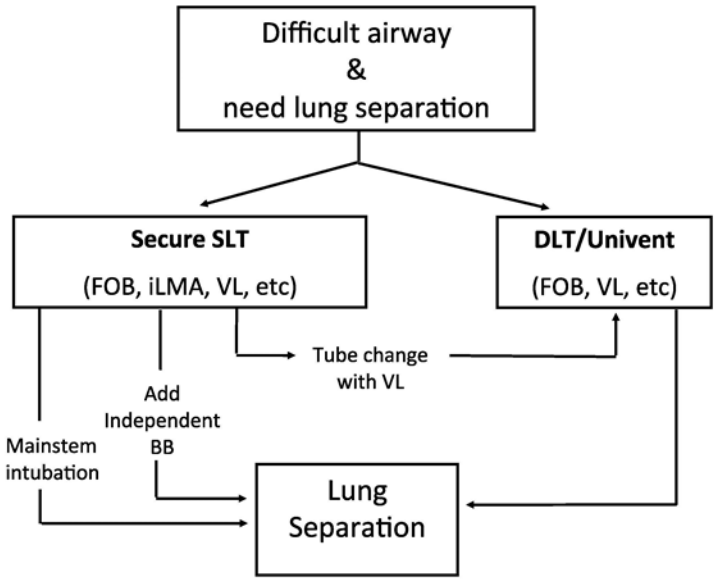

Figure 8. Approach to lung separation options in the patient with a difficult airway. *BB*, bronchial blocker; *FOB*, fiberoptic bronchoscope; *iLMA*, intubating laryngeal mask airway; *SLT*, single-lumen tube; *VL*, videolaryngoscope. From Klafta and Ovassapian.[47]

Upper and Lower Airway Difficulties

Airway difficulties may arise from the upper airway (more common) or the lower airway. Anatomical or pathological features of the upper airway that render conventional rigid laryngoscopy difficult for placement of SLTs are even more problematic for the placement of DLTs and Univent tubes because of their size and shape.[48] Awake fiberoptic intubation with an SLT or DLT may be the best option in cases of known or anticipated difficult intubation and ventilation.[21,47,49]

Lower airway difficulties can be encountered because of anatomical variation (*e.g.*, aberrant or supernumerary tracheal bronchi),[50] distortion of the tracheobronchial anatomy from prior surgery (*e.g.*, apically retracted left main bronchus following left upper lobectomy),[51] or strictures, extraluminal compression, or intraluminal masses. These changes may require creative solutions to lung separation and will influence the selection of the targeted bronchus and choice of a BB or DLT. Lower airway difficulties can be detected or predicted by diagnostic bron-choscopy before intubation or by imaging studies performed preoperatively.

Options for Lung Separation

Double-Lumen Tubes. The literature on videolaryngoscopy to facilitate DLT insertion has blossomed and now contains more comparative trials rather than just case reports or series. One recent study randomly allocated 60 patients *with normal airways* to intubation with a DLT using a GlideScope® (Verathon Inc., Bothell, WA) or Macintosh direct laryngoscope. Although duration of intubation was longer with direct laryngoscopy (63 *vs.* 46 sec), the success of the first intubation attempt (87% *vs.* 100%) was not significantly different.[52] Another 2012 study allocated 170 patients to DLT intubation with a Berg CEL-100 VL™ videolaryngoscope (Connell Energy Technology Co. Ltd., Shanghai, China) or Macintosh direct laryngoscope (this device has a 30-degree curve, whereas the GlideScope's is 60 degrees). These authors found similar intubation times but higher first attempt intubation success (93% *vs.* 79%) with the CEL-100.[53] Critical analysis of all such studies must consider

both patient characteristics (*e.g.*, average body mass indexes were all <|24), design features of the particular videolaryngoscope, and importantly, the experience of the operators with videolaryngoscopy and DLTs.[54]

Oral fiberoptic intubation with a DLT is well described in both awake and asleep patients.[49,55,56] A patient's mouth opening and oropharyngeal size must be large enough to accommodate a DLT for orotracheal intubation. Awake placement requires good topical anes-thesia, adequate conscious sedation, and assistance in maintaining soft tissue support. Soaking a DLT in a warm-water bath just before intubation and using sufficient lubrication will minimize its rigidity and has recently been shown to decrease the incidence of postoperative sore throat and vocal cord injuries (but not hoarseness).[57] Concurrent direct laryngoscopy may be required to elevate the supraglottic tissues to facilitate passage of a DLT through the glottic opening after the fiberoptic scope is in the trachea.[56] Videolaryngoscopy may add further benefit.[58]

Univent Tubes. Some anesthesiologists consider a Univent tube easier to place and position than a DLT,[59] particularly in patients with upper airway abnormalities.[60] The internal diameter of the ventilating lumen in a size 8.5 or 9.0 Univent tube will accommodate an adult 5.0 mm bronchoscope,[59] which then precludes the need to change tubes after diagnostic bronchoscopy. Although it is also suitable for fiberoptic intubation, the Univent tube has several limitations. First, unlike the polyvinylchloride of the SLT and DLT, the Univent tube is constructed of a polymeric silicone material that will not soften in a warm-water bath. As such, its curved shape is relatively fixed, and this may be a disadvantage when sliding it over a bronchoscope. Second, the fixed concavity often makes the leading edge of the tube impinge upon the vocal cords, impeding its passage into the trachea. A successful nasal intubation with a 7.0 Univent tube has been described, despite its size and rigidity.[61]

Endobronchial Blockers. See earlier discussion.

Single-Lumen Endotracheal Tubes. Using an SLT to intubate a main bronchus is another option for achieving lung separation and is frequently the preferred technique for children who are too small for DLTs or coaxial BBs.[62] Advantages of this approach include its simplicity and the rapidity with which lung separation can often be achieved, particularly when the right lung must be ventilated. Blind advancement of an SLT will rarely result in intubation of the left main bronchus, but rotating an *in situ* SLT 180° while turning the patient's head to the right will improve the success rate of left main bronchus intubation to about 92%.[63] Fiberoptic guidance of an SLT into the appropriate main bronchus is probably the easiest and most reliable technique. If significant amounts of blood or secretions preclude bronchoscopic visualization, using fluoroscopy to visualize and direct the radiopaque bronchoscope is another option.[64]

Disadvantages of the use of an SLT for lung separation include frequent exclusion of right upper lobe ventilation when an SLT is in the right main bronchus. Left upper lobe ventilation can also be excluded when the left main bronchus is relatively short.[65] Regardless of which lung is ventilated, neither independent suctioning nor application of continuous positive airway pressure to the nonventilated lung is possible. Lastly, if the nasotracheal route is used, most SLTs will not be long enough to provide reliable intubation of the main bronchus.

SLT to DLT Exchange. Exchange of an SLT for a DLT is a strategy commonly employed to achieve lung isolation when insertion of a DLT is difficult. In a simulator study comparing three different DLT designs, the Fuji-Phycon tube (Silbroncho®, Fuji Systems, Tokyo, Japan) was faster and easier to pass over an airway exchange catheter (AEC) than DLTs manufactured by Rüsch or Mallinckrodt when using an AEC plus GlideScope technique.[66] The authors attributed this difference to the Fuji-Phycon's more beveled bronchial tip, softer silicon material, and more angulated bronchial limb. Successful tube exchange is never a guarantee, especially when changing SLTs to DLT. A single-center retrospective analysis of 1,177 airway exchanges found an overall 13.8% failure rate, with 43 of 110 (39.1%) of SLT to DLT exchanges unable to be completed as intended.[67] Cook Critical Care manufactures AECs specifically designed for DLT exchanges. These differ from conventional AECs in that they are longer (100 cm), have centimeter markings that extend to 50 cm, and are extra firm with a 7-cm flexible tip. The 11F and 14F sizes will fit inside small and large DLTs, respectively.

Concurrent videolaryngoscopy will elevate the supraglottic tissues and provide visual guidance should the DLT need to be manipulated to successfully pass through the larynx. Continuous manual control of the AEC throughout

the entire exchange will help ensure it neither loses its intratracheal position nor advances too distally, causing trauma.

The Patient with a Tracheostomy

Although the presence of a tracheostomy greatly simplifies airway management for most anesthetics, it presents an interesting challenge when lung separation is required. As with orotracheal intubation, options include a DLT,[21] Univent tube,[68] or BB through the tracheostomy stoma. Depending upon the details of a patient's anatomy, such as stomal diameter, distance between the skin and the anterior tracheal wall, and stoma-to-carinal distance, DLTs and Univent tubes may be difficult to place and position precisely and atraumatically.

Another way to achieve lung separation in a patient with a tracheostomy is using a BB, either coaxially or alongside an SLT or tracheostomy tube through the stoma[69] or through the mouth.[70] Blind or bronchoscopically directed intubation of the main bronchus with an SLT inserted through the stoma is yet another option, although it has the usual limitations associated with intubations of the main bronchi. A short DLT specially designed for use with tracheostomies is available (Figure 9).[71]

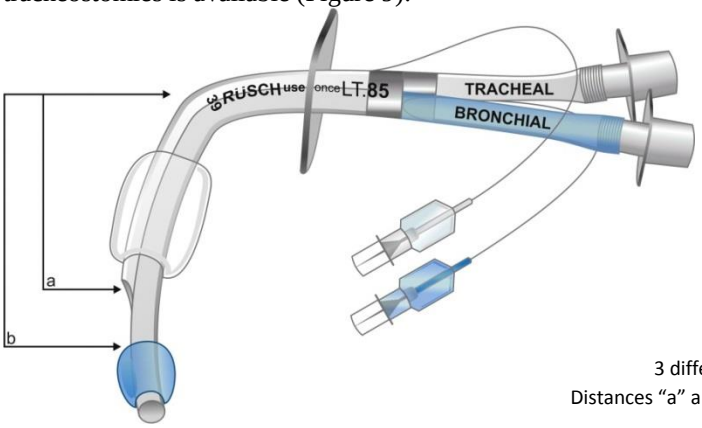

Figure 9. The Rüsch Tracheopart® (Teleflex, Morrisville, NC) double-lumen tube for a tracheostomized patient.

Extubation and Postoperative Intubation

When the decision is made to leave a patient intubated after a procedure involving lung separation, some special considerations need to be addressed. The possibility of the recurrent need for lung separation should be considered a reason to leave a patient intubated. Occasionally, an airway that was not difficult initially may become difficult after a lengthy procedure involving large fluids shifts that contribute to upper airway or head and neck edema. An anticipated need for postoperative intubation should therefore inform the preoperative choice of lung separation technique. If an SLT with a BB was used, then all that needs to be done at the end of the procedure is to remove the BB. If a Univent was used, then its blocker should be fully retracted and the Univent can function as an SLT.

If a DLT was used for lung separation, then the risks and benefits of changing to an SLT must be carefully weighed. The main advantage to leaving the tube in place is that the hazards associated with a tube change with a difficult airway are avoided. In this case, one can leave the tube positioned and ventilate both lungs through both lumens. Alternatively, the tube can be withdrawn to the point at which the tip of the bronchial lumen is just above the carina, which will position the tracheal cuff just below the vocal cords.[72] Increased flow resistance leading to obstructed expiratory flow or increased work of breathing is probably not clinically significant with 37F or larger Rüsch or Sheridan DLTs.[73]

CONCLUSION

Keys to success in one-lung anesthesia:

- Understand the physical details of DLTs and BBs. Select them appropriately.
- Use the fiberoptic bronchoscope! Optimize conditions (antisialagogue, suction), learn the tracheobronchial anatomy, and practice!
- Employ a "just seal" test every time. Avoid trouble and identify problems early.

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Improving First-Case of the Day On-Time Starts CAN Increase Operating Room Efficiency

Franklin Dexter, MD, PhD Iowa City, Iowa

Principles in Calculating Allocated OR Time for Use in Reducing Over-Utilized Time

Before I consider how improving first case of the day on-time starts can increase the efficiency of use of OR time, I need to address the question: what exactly is meant by "OR efficiency"? There are 3 simultaneous equations.

Suppose that the hours into which cases are scheduled in an OR have been calculated based on minimizing the expected inefficiency of use of OR time. Then, fewer than these allocated hours would be under-utilized OR time and greater than those allocated hours would be over-utilized OR time. For example, if the hours into which cases are scheduled in OR #1 are 7:15 AM to 3:30 PM, and the last case of the day ends at 1:30 PM, then there are 2 hours of under-utilized OR time from 1:30 PM to 3:30 PM.[1] Thus, there are 0 hours of over-utilized OR time. Conversely, suppose that the hours into which cases are scheduled in OR #2 are from 7:15 AM to 5:30 PM, and the last case of the day ends at 6:30 PM. Then, there is 1 hour of over-utilized OR time from 5:30 PM to 6:30 PM.[1] There are 0 hours of under-utilized OR time. These definitions for under-utilized and over-utilized OR time represent 2 of the 3 simultaneous equations.

The 3rd of the 3 equations is for the inefficiency of use of OR time itself. It equals the sum of two terms: (cost per hour of under-utilized OR time multiplied by the number of hours of under-utilized OR time) plus (cost per hour of over-utilized OR time multiplied by the number of hours of over-utilized OR time). Application of these 3 equations from operations research to OR management was figured out by Strum et al.[2]

These 3 equations have an implication. Suppose that the hours (above) into which cases were scheduled were chosen by committee decision (i.e., not by performing calculations to minimize the expected inefficiency of use of OR time). Then, there are not 2 hours of under-utilized OR time in OR #1 and 1 hour of over-utilized OR time in OR #2. For example, there is not, as far as I know, a name for the hours until 3:30 PM or past 5:30 PM, respectively. Be careful when you hear someone refer to "under-utilized" and "over-utilized" OR time. Hours are "under-utilized" and "over-utilized" only if compared to the allocated hours that minimize the inefficiency of use of OR time.

Continuing, OR workload for a service on a day of the week often follows a normal distribution.[2] Consequently, in principle (but, in practice, it is more involved mathematically), the inverse of the normal distribution function can be used to calculate the allocated OR time that maximizes OR efficiency.[2]

For example, suppose that, on Mondays, a hospital currently plans 3 ORs for orthopedics, each OR for 10 hours of cases (3 ORs x 10 hours = 30 hours). The total hours of orthopedic cases, including turnovers, follows a normal distribution with a mean of 30 hours. The relative cost of 1 hour of over-utilized OR time equals 2.0 multiplied by that of 1 hour of under-utilized OR time.[1,3] This is a typical value, being "time and a half" plus a bit extra for an intangible cost. With it being twice as expensive for finishing late rather than early, one wants to calculate the OR allocation that results in finishing early on 2/3rd of Mondays. That is the 66th percentile.

To apply the 66th percentile, consider a standard deviation of orthopedics' workload on Mondays, a typical value of 5 hours. In Microsoft Excel, use the following formula: "= NORMINV(2/3, 30, 5)". The answer that appears in the spreadsheet is 32.0 hours. Thus, the 66th percentile of the inverse of the cumulative normal distribution function with a mean of 30 hours and a standard deviation of 5 hours equals 32 hours. Using a mean of 30 hours, what OR allocation minimizes the inefficiency of use of OR time? 4 ORs with 8 hours of allocated time and 0 (zero) ORs with 10 hours of allocated time. The answer is not the mean of 30 hours.

{Note: this does **not** mean that the hospital "ought" to allocate 4 ORs for 8 hours. That depends on several factors such as the number of surgeons, whether there can be 4 ORs for 3 surgeons, etc.[1,3-5] Many papers and review articles have examined what to do in these more complicated but realistic situations. However, for understanding the principles of first case of the day starts, this simple approach is good enough.}

Suppose that the standard deviation of orthopedics' workload on Mondays is 10 hours (a larger than typical value). Since workload is assumed to follow a normal distribution, we again use the inverse of a normal distribution, and again use a ratio of 2.0: 1.0 for the cost of over-utilized: under-utilized OR time. In Excel, this is the formula: "= NORMINV(2/3, 30, 10)". Notice that the formula only differs from the one above in that the last number is now 10 instead of 5. This formula gives an answer of 34 hours (i.e., the 66th percentile of the normal distribution function with a mean of 30 hours and a standard deviation of 10 hours equaling 34 hours). Thus, for a mean of 30 hours, what OR allocation minimizes the inefficiency of use of OR time? It would be 3 ORs with 8 hours of allocated time and 1 OR with 10 hours of allocated time, because that sums to 34 hours. Comparing this result to the preceding one with 32 hours, because the variability in the workload among Mondays is greater (10 hours instead of 5 hours), the anesthesia group, facility, etc. should allocate greater hours of OR time. Doing so reduces the expected hours of over-utilized OR time, and that reduces the hours that anesthesiologists, nurses, etc., work late.[6]

Reducing Tardiness of First Case Starts Can Increase Efficiency of Use of OR Time

The remainder of the material depends principally on reducing the hours of over-utilized OR time. The reason why the preceding principles matter is because, as already stated, the hours in an OR beyond the allocated hours (i.e., hours into which cases are scheduled) are "over-utilized OR time" only if those allocated hours are the hours that minimize the inefficiency of use of OR time.

At a facility, OR nurses, nurse anesthetists, and anesthesiologists are full-time employees. The allocated time is from 7:00 AM to 3:00 PM. {I'm going to say this for the 3rd time, so that there is no misunderstanding; this means that the hours of OR time that minimize the inefficiency of use of OR time are to 3 PM.} Today, there happens to be 9.0 hours of cases scheduled in one OR. The other 4 ORs are estimated to end earlier. The intravenous catheter and regional nerve block are placed in the holding area from 6:25 AM to 6:55 AM, rather than in the OR as typical. The OR finishes at 3:30 PM instead of at 4:00 PM. Has this resulted in an increase in the efficiency of use of OR time?

As we approach the day of surgery, the cost of an hour of under-utilized OR time becomes negligible, relative to the cost of an hour of over-utilized OR time.[7,8] The terms related to the cost per hour of under-utilized OR time are no longer relevant. The remaining terms are only those related to over-utilized OR time. Continuing, the cost per hour of over-utilized OR time will differ among anesthesiologists, OR nurses, nurse anesthetists, surgeons, surgical technologists, etc. However, for each, it is a constant. The consequence is that for all the stakeholders, OR efficiency is maximized on the day of surgery by minimizing the hours of over-utilized OR time.[7,8]

Returning to the scenario, the allocated time was from 7:00 AM to 3:00 PM. Having the existing personnel target the OR with the largest hours of cases resulted in the cases finishing in 8.5 hours instead of the expected 9.0 hours. What was sustained was 0.5 hours of over-utilized time instead of 1.0 hours of over-utilized time. Thus, reducing the time to incision of the first case of the day increased OR efficiency. Working faster early in the day definitely can increase OR efficiency.

Suppose, on the other hand, that the allocated OR time was from 7:00 AM to 4:30 PM. Then, even if the cases finished at 4:00 PM, there would not be over-utilized OR time. The same clinical intervention has not resulted in an increase in OR efficiency.

What this shows is that working quickly is <u>not</u> synonymous with being efficient. Rather, working quickly <u>can</u> increase efficiency, and whether efficiency is increased depends on the longer-term management decisions (i.e., those of the preceding section). That is why the preceding section matters. Good OR management operational decision-making on the working day before (and on) the day of surgery is highly sensitive to the OR allocations, which is why those values need to be calculated appropriately.[5,6]

Before investing financially in a lean initiative to improve on-time starts, I strongly recommend performing the full analysis.[1] That is what we published in our 2006 review article.[1] However, there is a simpler and usually suitable approach for screening for cost saving opportunities that result from improving on time starts. Suppose that the briefest period of staff scheduling is for 8.5 hours (i.e., a typical US value). Then, for ORs with less than or equal to 8 hours of cases, there would generally be no savings from reducing tardiness of first case starts.[9,10] The reason is that there will not be any over-utilized OR time, because the briefest allocated OR time would be 8 hours. {This is part of the real-world complexity I mentioned in the first section}. For ORs with greater than 8 hours of cases, each 1.0-minute reduction in tardiness reliably results in a savings of greater than 1 minute of regularly scheduled time.[9,10] One simulation method (study) showed 1.1 minutes while another showed 1.2 minutes.[9,10] This savings

is principally achieved by reducing the allocated OR time.[9] That is a very important finding and principle. Often managers, clinicians, etc., think short term in relation to cost savings rather than to consider how staff scheduling can be adjusted long term. Reducing the tardiness of first case starts *can* increase OR efficiency and very often does so, but not by making a difference "today." Rather, it is by progressive, long-term changes in staff scheduling.

The full analysis of the cost savings realized by reducing tardiness of first cases of the day is the same as the analysis of turnover times.[1] Suppose that an OR has 3 cases and the first case of the day enters the OR 8 minutes late. This is the same as increasing the mean turnover time by 4 minutes.[1,9] The analysis is performed for each combination of service and day of the week. The review article shows that for multiple services and days of the week, at the Australian hospital studied, reducing tardiness of the first case of the day produced a large cost savings.[1]

Perceptions, biases, and physicians' roles

The preceding information essentially suggests targeting ORs with expected over-utilized time for reduction in tardiness of the first case of the starts. But, what about the other ORs? Do nurses, anesthesiologists, etc., in ORs with substantial under-utilized OR time slow down (e.g., to prevent add-on cases). No: Such behavior is not what is observed in practice.[4] There is a very slight but significant effect in the opposite direction ($P = 0.008$). The reason for this is that, on days with substantial under-utilized time, there are more providers available to help in other ORs.[4] Furthermore, only 1% of the variance in tardiness among first cases is attributable to anesthesiologists; there are generally not significant differences in tardiness among anesthesiologists when controlling for specialty.[9]

The most common cause of late first case of the day starts is tardiness of the surgeons.[11-15] Time series models of progressive changes over months in tardiness of first case starts show that anesthesiologists respond to greater on-time readiness of nurses and equipment, with a lag of 1 month ($P = 0.005$).[12] Surgeons respond to greater on-time readiness of anesthesiologists, nurses, and equipment, with a lag of 2 months ($P < 0.0001$).[12] This is, in my opinion, one of the classic studies in the application of operations research and management science to OR management. Quoting the authors: "These results contradict the Pareto principle: surgeons are the main cause of delay for first surgeries but one should not focus on them. It is the first source of the chain that needs to be closely controlled rather than the one which appears to cause the most delays."[12] The lesson is not just for handling first case starts,[12] but essentially all operational type problems in OR management.[16] Unless a facility has research-level accurate data and analysts who are going to perform the analyses as in the scientific papers, one should rely principally not on internal data and analysis, but on the results of those papers.[16] There is no additional effort required to do the literature search in order to find those papers because one cannot know if the facility has accurate data or has performed the appropriate analyses without having read the papers. Reference (16) reviews how to find OR management articles.

Why are these behavioral results counter-intuitive? Most anesthesiologists, OR nurses, surgeons, etc., lack scientific knowledge of over-utilized OR time ($P < 0.0001$).[17] When we studied why this was so, we found that the material in the first section could not be learned simply through the experience of working in ORs.[17] Also, most survey respondents falsely believed that 10 minutes of tardiness of the first case causes subsequent cases in the OR to start at least 10 minutes late ($P < 0.001$).[17] Most respondents did not know that most cases take less time than scheduled ($P = 0.008$).[17] Even among those respondents who did know that most cases take less time than scheduled, not a single one applied that knowledge to infer that 10 minutes of tardiness of the first case start time does not cause subsequent cases to start at least 10 minutes late ($P = 0.0002$).[17] This is an example of a "cognitive bias." The importance of this observation is that institutional fixation on first cases of the day is immutable to education.[17] Such cognitive biases are amplified by small groups (i.e., a surgical committee is less likely to make evidence-based decisions than a scientifically knowledgeable manager).[18,19] The route to achieving rational goals is to rely on a manager to make decisions autocratically while relying on the operations research (mathematical) type decisions.[19] Knowledgeable physician leadership matters.[20]

One way managers can improve on-time starts, and thus increase OR efficiency, is by providing electronic displays with evidence-based recommendations for use on the working day before surgery and the day of surgery.[21] As described in the 1st section, by definition, such displays need to incorporate OR allocations calculated based on maximizing efficiency of use of OR time.[21] The manager can insure that staff take courses (i.e., receive education), which increases trust in the manager's recommendations.[21,22] When monitoring a manager's performance, a good criterion for evaluating the manager's facility is whether the displays effectively provide recommendations and

checklists for how to use the information.[23] The anesthesia group-facility agreement can be used to codify the performance criteria.[20,24]

Achieving the reductions in time for use to increase OR efficiency: Notifications on the day of surgery

When each patient's information was reviewed repeatedly, and an escalating notification system was used to contact each team member to attend to pending tasks, first case start delays were reduced significantly ($P < 0.001$).[14] Similarly, patient care assistants were notified 45 minutes before OR start time to go to the selected ICU bed and prepare the patient for transport.[25] The anesthesia provider was notified 15 to 20 minutes ahead of surgery for patient communication handoff with the ICU RN.[25] These notifications significantly reduced mean tardiness ($P < 0.0001$).[25]

Achieving reductions in time for use to increase OR efficiency: Planning the working day before surgery

At facilities where anesthesiologists medically direct multiple ORs, they must effectively use staggered starts (≅ 20 minutes to incision) during first cases of the day, since otherwise they cannot be present at all critical portions of the cases.[26] With 1:3 MD:CRNA, and medical direction, lapses would occur on greater than 96% of the days.[26] Therefore, as feasible, surgeons should be notified in advance which ORs will be the 3rd to start, so that those with later starts are not waiting in the ORs.[27] This can be done, because anesthesiologists are good at forecasting time from OR entrance until start of positioning.[28] Times differ depending primarily on anesthetic technique (e.g., general), the patient's American Society of Anesthesiologists' Physical Status, and the procedures to be done (e.g., arterial line placement).[29]

Teaching anesthesiology residents increases OR time before the start of surgery by a mean of 4 minutes.[30,31] Anesthesiologists are faster when not supervising multiple ORs.[32] Therefore, as appropriate and feasible, anesthesiologists practicing alone should be assigned to the ORs with over-utilized time, and 1st and 2nd year anesthesiology residents to ORs with substantial under-utilized OR time.[33]

Assigning sufficient numbers of anesthesiologists and support personnel to perform peripheral nerve blocks before OR entrance can reduce tardiness of first case starts.[34,35] As feasible, cases within surgeons' lists should be sequenced so that more cases with peripheral nerve blocks are performed later in the workday. Such sequencing does not increase the incidence of days with delayed PACU entrance.[36]

Surgical residents in specific specialties should have systems in place to assure no or small tardiness of starts, as relevant.[37] An example is having a mid-level resident leave team rounds early when rounds are taking sufficiently long as to influence first case start.[37] Another example is having surgical residents start morning rounds earlier, when needed, so that at least one resident can assure that site marking and surgical consent have been completed at least 30 minutes before the scheduled start time of each of the first cases of the day of their service.[38]

For an OR to be used for patients who were admitted preoperatively, the case most likely to start on time should be scheduled to be the first case start, changing it only if there is a new, emergency case.[39] This practice reduced the mean tardiness of first case starts of the trauma list by 26 minutes ($P < 0.001$).[39]

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Strategies to reduce cardiac risk for noncardiac surgery

Lee A Fleisher, M.D. **Philadelphia, PA**

In 2014, the American Heart Association/American College of Cardiology (AHA/ACC) Guidelines on Perioperative Cardiovascular Evaluation before Noncardiac Surgery were updated which included a new algorithm and new recommendations regarding perioperative beta-blockade usage.[1] In addition, the European Society of Cardiology (ESC) has also produced Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery.[2] These recommendations are similar to the AHA/ACC recommendations with an algorithm, and the AHA/ACC and ESC discussed their recommendations prior to simultaneous publication in order to ensure that the any differences in recommendations were fully vetted. In 2017, the Canadian Cardiovascular Society Guidelines was published which has some differences in medication management and postoperative surveillance compared to the other Guidelines.[3] The AHA/ACC Guidelines were update in 2016 to address the issue of Dual anti-platelet therapy (DAPT) after coronary stent placement.[4]

The basic tenet in preoperative evaluation remains that information regarding the extent and stability of disease will effect patient management and lead to improved outcome. In the case of cardiovascular disease, the preoperative evaluation attempts to define the extent of coronary artery disease and the left ventricular function.

Clinical Assessment

Clinical risk indices are advocated to establish baseline cardiovascular risk with 1% being the rate of major adverse cardiac events (MACE) above which testing can be considered. The Revised Cardiac Risk Index (RCRI) includes six independent predictors: high-risk type of surgery, history of ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, preoperative treatment with insulin, and preoperative serum creatinine >2.0 mg/d, with elevated risk being 2 or more risk factors.[5] Alternatively, a risk calculator was developed using data from the American College of Surgeons National Surgical Quality Improvement Project (ACS-NSQIP). (http://site.acsnsqip.org)[6] The authors found that theACS NSQIP surgical risk calculator was a decision-support tool which can be used to estimate the risks of most operations. The advantage of the ACS-NSQIP risk calculator is that it incorporates both clinical and surgical risk.

A thorough history should focus on cardiovascular risk factors and symptoms or signs of unstable cardiac disease states, such as myocardial ischemia with minimal exertion, active congestive heart failure, symptomatic valvular heart disease, and significant cardiac arrhythmias. Patients with a prior MI have coronary artery disease, although a small group of patients may sustain an MI from a nonatherosclerotic mechanism. A recent analysis using Medicare Claims data suggests that the risk of reinfarction remains high for at least 2 months after an MI, and that coronary artery bypass grafting (CABG) may reduce that risk while coronary stent placement soon after an MI does not.[7, 8] The current Guidelines have adopted the 60 day recommendation.

Importance of Surgical Procedure

The surgical procedure influences the extent of the preoperative evaluation required by determining the potential range of changes in perioperative management. There is little hard data to define the surgery specific incidence of complications, and the rate may be very institution dependent. Eagle et. al. published data on the incidence of perioperative myocardial infarction and mortality by procedure for patients enrolled in the coronary artery surgery study (CASS).[9] Higher risk procedures for which coronary artery bypass grafting reduced the risk of noncardiac surgery compared to medical therapy include major vascular, abdominal, thoracic, and orthopedic surgery. Ambulatory procedures denote low risk. Vascular surgery represents a unique group of patients in whom there is extensive evidence regarding preoperative testing and perioperative interventions. Endovascular stent placement is associated with lower perioperative risk, particularly the risk of death, but similar long-term mortality compared to open procedures. The current Guidelines combined the previous high and intermediate surgical risk categories. The ACS-NSQIP risk calculator incorporates surgical specific risk and therefore has more discriminatory ability. There is evidence to suggest that the rate of surgical mortality is correlated with hospital surgery-specific volume and therefore higher volume hospitals may have better outcomes which can impact the decision to perform preoperative testing. Locations with less intensive resources, eg. smaller hospitals, may actually perform testing to determine who to refer to larger Centers.

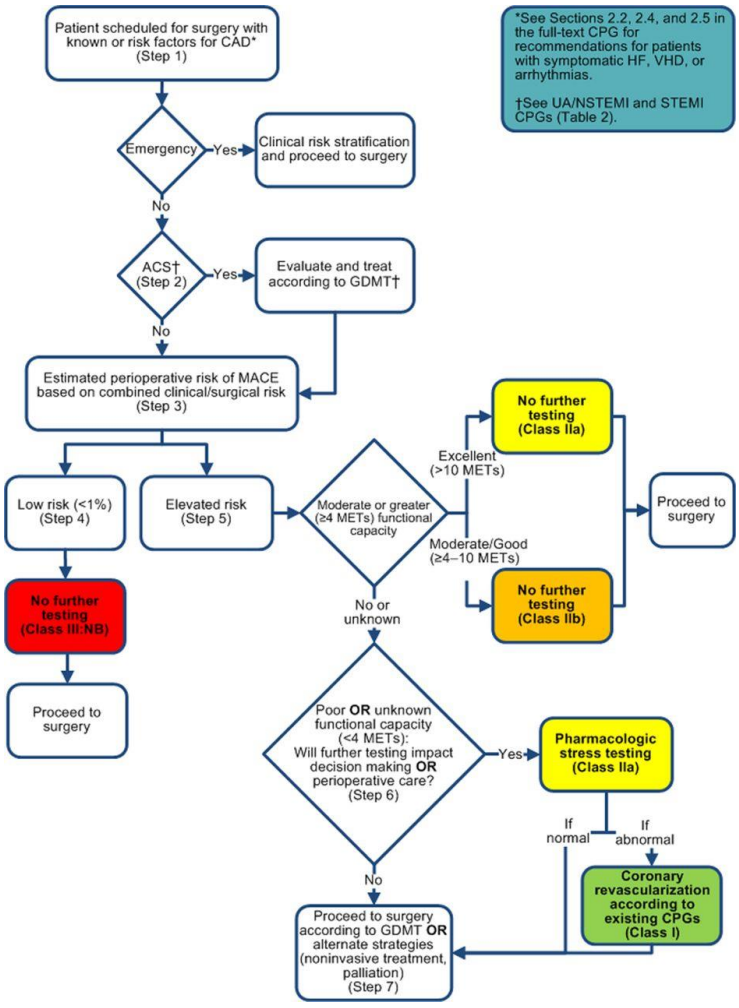
Importance of exercise tolerance

Exercise tolerance is one of the most important determinants of perioperative risk and the need for invasive monitoring. If a patient can walk a mile without becoming short of breath, than the probability of extensive coronary artery disease is small. Alternatively, if patients become dyspneic associated with chest pain during minimal exertion, then the probability of extensive coronary artery disease is high. Reilly and colleagues demonstrated that the likelihood of a serious complication occurring was inversely related to the number of blocks that could be walked or flights of stairs that could be climbed.[10] Exercise tolerance can be assessed with formal treadmill testing or with a questionnaire that assesses activities of daily living. There is some suggestion that cardiopulmonary testing is useful for more accurately predicting risk.

Approach to the Patient

The figure presents in algorithmic form a framework for determining which patients are candidates for cardiac testing for ischemic heart disease.[1] Given the availability of this evidence, the AHA/ACC Writing Committee chose to include the level of the recommendations and strength of evidence for many of the pathways. Importantly, the value of adopting the algorithm depends upon local factors such as current perioperative risk and rate of utilization of testing.

The new algorithm combines clinical and surgical risk (figure to right). Those at low risk (<1% Major Adverse Cardiac Events (MACE)) proceed to surgery. The new approach collapses intermediate and high risk into one category of elevated risk. If the patient has moderate or greater exercise capacity then the patient should proceed to surgery. In patients with poor exercise capacity, the key question is whether further testing will change management. A key change in the new algorithm is the incorporation of noninvasive treatment or palliation as one of the potential rationales for testing.

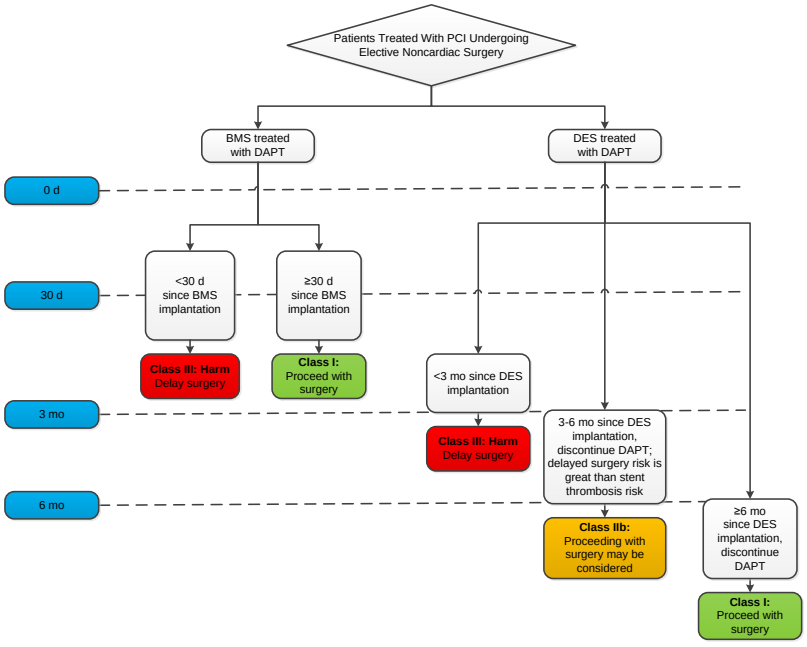


Interventions for patients with documented CAD

There is increasing evidence that coronary revascularization before noncardiac surgery does not reduce the incidence of perioperative cardiac morbidity. McFalls and colleagues reported the results of a multi-center randomized trail in the Veterans Administration Health System in which patients with documented coronary artery disease on coronary angiography (CARP), excluding those with left main disease or severely depressed ejection fraction (<20%), were randomized to coronary artery bypass grafting (CABG)(59%) or percutaneous coronary interventions (PCI)(41%) versus routine medical therapy.[11] At 2.7 years after randomization, mortality in the revascularization group was not significantly different (22%) percent compared to the no-revascularization group (23%) percent. Within 30 days after the vascular operation, a postoperative myocardial infarction, defined by

elevated troponin levels, occurred in 12 percent of the revascularization group and 14 percent of the no-revascularization group (P=0.37). In a follow-up analysis, Ward and colleagues reported improved outcome in the subset who underwent CABG compared to PCI.[12] When patients who underwent coronary angiography in both the randomized and nonrandomized portion of the CARP trial, only the subset of patients with unprotected left main disease showed a benefit with preoperative coronary artery revascularization.[13] This finding was supported by that of Poldermans and colleagues who randomized 770 patients having major vascular surgery and considered as having intermediate cardiac risk, defined as the presence of 1 or 2 cardiac risk factors to either undergo further risk stratification with stress imaging or proceed right to surgery.[14] All patients received preoperative bisoprolol with a targeted heart rate (HR) of 60-65 initiated before, and continued after surgery. The 30 day incidence of cardiac death and non-fatal MI was similar in both groups (1.8% in the no testing group versus 2.3% in the tested group).

The current evidence does not support the use of percutaneous transluminal coronary angioplasty (PTCA) beyond established indications for nonoperative patients, since the incidence of perioperative complications does not appear to be reduced in those patients in whom PTCA was performed less than 90 days prior to surgery.[15, 16] Coronary stent placement may be a unique issue and several studies suggest that a minimum of 30 days is required before the rate of perioperative complications is low.[17, 18] Several reports suggest that drug-eluting stents (DES) may represent an additional risk over a prolonged period (up to 12 months), particularly if antiplatelet agents are discontinued.[19] However, newer studies suggest that surgery may be same in DES if performed within 3-6 months of surgery.[20-22] The 2016 DAPT Guidelines (figure below) suggest continuing aspirin therapy in all patients with a coronary stent and discontinuing clopidogrel for as short a time interval as possible for patients with bare-metal stents <30 days or drug-eluting stents <6 months; with DAPT can be discontinued.[4]



Based upon the non-perioperative literature, there is a suggestion that hold clopidogrel for the traditional 8 days may actually increase risk associated with a hypercoagulable rebound suggesting a shorter period of time may be optimal. A recent cohort study suggests that withdrawal of anti-platelet agents >5 days is associated with increased major adverse cardiac events.[23]

There is now a great deal of evidence to suggest that perioperative medical therapy can be optimized in those patients with coronary artery disease as a means of reducing perioperative cardiovascular complications. Multiple studies have demonstrated improved outcome in patients given perioperative beta-blockers, especially if heart rate is controlled, acknowledging the previously discussed concerns regarding the quality of the studies from the Erasmus group.[24, 25] Subsequent studies demonstrated that beta blockers may not be effective if heart rate is not well controlled, or in lower risk patients.[26-28] The POISE trial was published in which 8351 high-risk beta-blocker naive patients were randomized to high dose metoprolol CR versus placebo.[29] There was a significant reduction of the primary outcome of cardiovascular events, associated with a 30% reduction in MI rate, but with a significantly increased rate of 30-day all-cause mortality and stroke. Several recent cohort studies continue to support the fact that high risk patients on beta-blockers were associated with improved outcome. A Canadian administrative dataset suggests that the perioperative morbidity was higher if beta-blockers were started within 7 days as compared to 8 days or greater. As part of the update to the current ACC/AHA Guidelines, an Evidence Review Committee was formed to independently review the data on perioperative beta-blockade. Perioperative

beta blockade started within 1 day or less before noncardiac surgery prevents nonfatal MI but increases risks of stroke, death, hypotension, and bradycardia.[30] Without the controversial DECREASE studies, there are insufficient data on beta blockade started 2 or more days prior to surgery. Wallace et al. reported that perioperative β-blockade administered according to the Perioperative Cardiac Risk Reduction protocol is associated with a reduction in 30-day and 1-yr mortality. [31] Perioperative withdrawal of β-blockers is associated with increased mortality. The current ACCF/AHA Guidelines on perioperative beta-blockade advocate that perioperative beta-blockade is a Class I indication and should be used in patients previously on beta-blockers. The new recommendations changed the recommendation from a Class IIa to IIb for patients undergoing vascular surgery who are at high cardiac risk owing to coronary artery disease or the finding of cardiac ischemia on preoperative testing.

Other pharmacologic agents have also been shown to improve perioperative cardiac outcome. In POISE II, Alpha-2 agonists were not shown to improve perioperative outcome.[32] POISE II also evaluated the effectiveness of aspirin therapy in a cohort of patients without a recent stent. Administration of aspirin before surgery and throughout the early postsurgical period had no significant effect on the rate of a composite of death or nonfatal myocardial infarction but increased the risk of major bleeding.[33] Most recently, perioperative statins have been shown to improve cardiac outcome. Durazzo and colleagues published a randomized trial of 200 vascular surgery patients in which statins were started an average of 30 days prior to vascular surgery.[34] A significant reduction in cardiovascular complications was demonstrated using this protocol. Le Manach and colleagues demonstrated that statin withdrawal greater than 4 days was associated with a 2.9 odds ratio of increased risk of cardiac morbidity in vascular surgery.[35] The Guidelines advocate continuing statin therapy in patients currently taking statins as a Class I indication. A multi-modal approach to medical management should be taken in high risk patients.

There continues to be controversy regarding the optimal management of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB). In the Veterans Administration, withholding ARB postoperatively is strongly associated with increased 30-day mortality, especially in younger patients, although residual confounding may be present.[36] In the VISION trial, compared to patients who continued their angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, the ACE/ARB users who withheld their agents in the 24 h before surgery were less likely to suffer the primary composite outcome of all-cause death, stroke, or myocardial injury; adjusted relative risk, 0.82; 95% CI, 0.70 to 0.96; P = 0.01) and intraoperative hypotension (adjusted relative risk, 0.80; 95% CI, 0.72 to 0.93; P < 0.001).[37] The current AHA/ACC Guidelines suggest that continuation of ACE inhibitors or angiotensin-receptor ARBs perioperatively is reasonable, but should be restarted as soon as reasonable. The new study questions this recommendation but further randomized trials are needed.

Summary

Preoperative evaluation should focus on identifying patients with symptomatic and asymptomatic coronary artery disease and the exercise capacity of the patient. The decision to perform further diagnostic evaluation depends upon the interactions of patients and surgery specific factors, as well as exercise capacity and should be reserved for those at elevated risk with poor exercise capacity. The indications for coronary interventions are the same in the perioperative period as for the non-operative setting. New recommendations for DAPT have been proposed which suggest discontinuation and noncardiac surgery at 6 months after stent placement.

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ANESTHESIOLOGY 2017
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Patient Blood Management: Improving both sides of the value equation

American Society of Anesthesiologists Annual Meeting Refresher Course Lecture

Daryl J. Kor, M.D.
Mayo Clinic
Rochester, Minnesota 55905

Introduction

Preoperative anemia has been consistently associated with adverse perioperative outcomes in patients undergoing both cardiac and non-cardiac surgical procedures.[1] Historically, red blood cell (RBC) transfusion was viewed as an effective and acceptably safe intervention for the management of anemia. Similarly, platelet and plasma therapies have been viewed as safe and necessary interventions for the management of thrombocytopenia and altered coagulation parameters, respectively. However, blood transfusion has more recently come under increased scrutiny.[2-4] The three primary drivers of this renewed concern relate to questionable efficacy of some transfusion practices for the major blood component therapies (red blood cells, plasma, platelets);[5-7] underappreciated risks of blood transfusion, including life-threatening respiratory complications such as Transfusion-Related Acute Lung Injury and Transfusion-Associated Circulatory Overload;[8-10] and increased recognition of the substantial associated health care costs (estimated to exceed $10 billion in the US for RBC transfusions alone).[11-13] In aggregate, these concerns have resulted in increased interest in the optimization of patient's blood health as well as transfusion practice.

In this refresher course lecture, we will outline the current state of blood component utilization and patient blood management (PBM) with specific emphasis on the perioperative environment. We will further identify gaps in our current understanding relating to both the risks and benefits of transfusion therapies and we will advocate for PBM as a cornerstone for optimizing future transfusion practices. The presentation will provide specific examples of PBM approaches that have led to meaningful change in transfusion practice with substantial impact of the quality of care delivered.

Perioperative Anemia

Background and Epidemiology

Anemia is defined as a total reduction in erythrocyte number, reduced amount of circulating hemoglobin, or decreased circulating red blood cell mass, resulting in a pathological state where the oxygen-carrying capacity of blood is insufficient to meet physiological demand. The World Health Organization defines anemia as a hemoglobin level of less than 12.0 g/dL in non-pregnant adult women, less than 11.0 g/dL in pregnant adult women and less than 13.0 g/dL in adult men.[14]

Anemia is a common finding in pre-operative patients, with a prevalence ranging from 5% to 76% depending on patient age, presenting condition, and the planned operation.[15] Several large observational studies have associated preoperative anemia with increased risk of perioperative morbidity and 30-day postoperative mortality. Evidence further suggests the utilization of RBC transfusion to treat anemia further contributes to increased perioperative morbidity and mortality. The administration of RBC transfusion for the treatment of anemia has also been associated with increased cost when compared with preoperative elevation of the hemoglobin concentration with pharmacologic interventions (e.g., erythropoiesis-stimulating agents).[1]

Management of Preoperative Anemia

The American Society of Anesthesiologists Task Force on Perioperative Blood Management recommends erythropoietin with or without iron as an effective measure for reducing patient's exposure to allogeneic RBC transfusions (Category A1-B evidence).[16] In contrast, the task force notes insufficient evidence to evaluate the efficacy of erythropoietin with iron compared with erythropoietin without iron. Furthermore, equivocal findings were noted when comparing preadmission iron supplementation to either placebo or no iron with the outcomes of preoperative hemoglobin levels and perioperative allogeneic RBC transfusions (Category A2-E evidence).[16]

Red Blood Cell Transfusion

Background and Epidemiology

The number of RBC units transfused annually approaches 14 million in the United States alone.[17] More than a quarter of these transfusions occur in the perioperative environment. Despite a growing number of clinical trials and evidence-based guidelines supporting restrictive RBC transfusion policies, liberal RBC transfusion practices remain commonplace. Furthermore, there remains tremendous variability in RBC transfusion practices, both for cardiac and non-cardiac surgical procedures.[18,19]

From a physiologic perspective, RBC transfusions are administered with the intent of improving end-organ oxygenation. Interestingly, the majority of basic physiologic studies fail to show improvements in physiologic parameters such as oxygen consumption or lactate clearance following RBC transfusion.[20]

RBC transfusion guidelines

A growing body of clinical trials evaluating RBC transfusion practices has now been completed and their results published. Although a recent clinical trial suggested the potential for improved outcomes with more liberal RBC transfusion practices in the setting of cardiac surgery,[21] the vast majority of trials support the safety of more conservative RBC transfusion practices.[22] These results appear robust, with similar results being consistently reported in a variety of surgical and medical populations including those undergoing Orthopedic and Cardiac Surgery, as well as those with traumatic brain injury, sepsis, and more heterogeneous critically ill populations.[23-28] In sum, the preponderance of data (both observational and experimental) support the implementation of restrictive RBC transfusion practices in hemodynamically stable, non-hemorrhaging patients.

Current guidelines recommend a hemoglobin threshold of 7 g/dL for RBC transfusion in hemodynamically stable, non-bleeding patients.[29] A higher threshold of 8 g/dL is often recommended for those with documented coronary artery disease or symptomatic anemia (e.g. active ischemia; orthostatic hypotension, syncope or tachycardia unresponsive to fluid therapy; congestive heart failure). For actively bleeding patients, RBC transfusion decisions should be based on the overall clinical context rather than strict adherence to a specific hemoglobin threshold.

Plasma

Background and Epidemiology

Nearly 4 million units of plasma are transfused each year in the United States alone.[17] A large proportion of these transfusion episodes occur in the perioperative environment, particularly in the setting of cardiac surgery. Despite efforts to educate care providers on the appropriate indications for plasma administration and limit the number of inappropriate transfusions, liberal plasma transfusion practices remain common. Indeed, it has been suggested that up to 50% of plasma transfusions occur outside of published guidelines,[30,31] with the most commonly cited reason for plasma transfusion being the correction of abnormal coagulation tests prior to an elective invasive procedure.[32] Importantly, the preponderance of studies performed to date have failed to show a consistent correlation between mild-to-moderate coagulation abnormalities [i.e. International Normalized Ratio (INR) $\leq$ 2] and bleeding complications in patients undergoing elective invasive percutaneous procedures.[7,33] In addition, plasma transfusion does not reliably normalize mild-to-moderate elevations in the INR.[34] As studies have failed to demonstrate a clear relationship between mild-to-moderate elevations in INR and increased procedural bleeding, plasma administration aimed at normalizing an elevated INR for the prevention of bleeding complications remains theoretical at best. Indeed, the available literature does not support prophylactic plasma transfusion in this setting.[11]

Plasma Transfusion Guidelines

Perioperative plasma product transfusion guidelines were recently published by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies.[16] Indications for plasma administration in the perioperative setting include active bleeding related to coagulation factor deficiencies for which specific concentrates are not available as well as trauma-related massive hemorrhage as part of a fixed-ratio transfusion resuscitation protocol (e.g., 1:1:1, RBC:plasma:platelet). Additional clinical scenarios where plasma therapy may be warranted include the reversal of warfarin anticoagulation in a patient with active bleeding or need

for emergency surgery (when prothrombin complex concentrates are not available) or the correction of excessive microvascular bleeding in the presence of an INR > 2.0. Plasma administration is also recommended as a replacement fluid when providing plasmapheresis for specific clinical indications (e.g., thrombotic thrombocytopenic purpura). As noted above, plasma transfusion is not recommended for the treatment of mild-to-moderate elevations in the INR (INR $\leq$ 2) when clinically significant bleeding is not present.

Platelets

Background and Epidemiology

More than 2 million platelet units were transfused in in the US in 2011.[17] This number represents a 7% increase in platelet utilization when compared to 2008 and continued a steady trend of increased annual platelet utilization. An estimated 20-25% of these platelet transfusions occur in the perioperative environment with the majority being delivered in the setting of cardiac surgery.[17] In the recent observational study of Glance et al. evaluating patients undergoing non-cardiac surgery, thrombocytopenia was present in 1 in 14 patients without clinical indications for preoperative platelet testing.[35] Thrombocytopenic patients were more likely to be transfused and had higher 30-day mortality when compared to those with normal preoperative platelet counts. Less clear is the impact of perioperative platelet transfusion on mitigating these risks. A recent large observational study in the setting of non-cardiac surgery failed to identify reductions in bleeding complications or improved clinical outcomes when comparing those who received preoperative platelet transfusions to those who did not.[36] Similar findings were also recently noted in the setting of percutaneous procedures.[37]

Platelet Transfusion Guidelines

Although a number of clinical trials have evaluated platelet transfusion thresholds in the setting of hematologic disorders in patients undergoing chemotherapy or stem cell transplantation, surprisingly few studies have evaluated the impact of platelet transfusion on bleeding complications in the perioperative environment.[6] For those with hematologic disorders, platelet counts of 10 x 10^9/L (20 x 10^9/L for those on heparin or with evidence of increased platelet destruction) are advocated as transfusion thresholds. Although similar trials have not been performed in the perioperative setting, most guidelines recommend a platelet count transfusion threshold of 50 x 10^9/L (100 x 10^9/L for procedures involving a closed anatomic space) in this environment.[16] A lower threshold of 20 x 10^9/L is recommended for prophylactic platelet transfusion in a patient undergoing an elective central line placement (although lower platelet counts may be safely tolerated if the venous puncture site is compressible [e.g., internal jugular, femoral] and real-time ultrasonography is being used). Of note, evidence supporting the efficacy of platelet transfusion for the reversal of antiplatelet medication effects is very limited, and significant uncertainty remains regarding the benefit of this practice.[6,38]

Transfusion Risks

As with all medical therapies, blood transfusion is not without risk. Historically, concerns have been centered on the vertical transmission of infectious disease. Although significant progress has been made in mitigating the risk of transfusion-associated infectious complications, additional risks have since come to light. Transfusion-Related Acute Lung Injury (TRALI) remains the leading cause of transfusion-related death in the U.S.[10] This is closely followed by a second transfusion-related pulmonary complication known as Transfusion-Associated Circulatory Overload (TACO). While the incidence of TRALI is believed low (< 1%), the condition has significant associated mortality, estimated to range from 15-20%.[39] TACO is a more frequent complication with an estimated incidence of approximately 4%.[8] Though TACO's attributable mortality is less well defined, clear associations with increased respiratory support requirements, intensive care unit admission, and length of hospital stay have been noted.[8] Importantly, a growing body of literature has begun to highlight concerns associated with under-diagnosis and under-reporting for both TRALI and TACO.[40]

Additional transfusion-related complications can include febrile transfusion reactions (the most common transfusion-related complication with rates reported up to 30% with platelet transfusions), allergic and anaphylactic reactions, hypotensive transfusion reactions, and hemolytic transfusion reactions (acute and delayed). Additional rare transfusion complications include transfusion-associated sepsis, graft-versus-host disease and post-transfusion purpura.

Transfusion Costs

Expenses related to the acquisition of a blood component (acquisition costs) represent a fraction of the overall costs associated with a transfusion episode. Additional transfusion-related costs include those associated with labor, component processing and storage, and supplies for storing, testing, and administering the blood component. These 'activity-based' or 'direct variable' costs have been quantified for both red blood cell and plasma transfusions.[12,13,41] Results of these analyses suggest that total transfusion costs can be up to 4.8-fold greater than the cost of simply acquiring the blood component. Notably, these cost considerations also fail to account for expenses related to transfusion-related adverse events. Regardless, with an estimated cost of $761 per RBC unit (activity-based costs), it is estimated that total annual RBC transfusion expenditures may approach $10.5 billion in the US alone.[17,41] Prior observational studies have associated liberal perioperative transfusion practices with significant excess perioperative costs.[42] Similarly, after adjusting for potentially confounding variables, the administration of transfusion(s) to multiday acute care inpatient admissions was associated with 1.83 fold higher mean inpatient cost.[43] Though the precise impact of PBM activities on overall institutional economics is often be difficult to determine, it is clear that the impact can be significant.

Transfusion Education

Perioperative training programs have done a poor job of incorporating PBM education into the medical curriculum. It has been reported that less than 20% of Anesthesiology residents receive formal training in PBM.[17] The frequency of formal training in best transfusion practice is only slightly improved at institutions with PBM programs, estimated at less than 30%.[17] Similar numbers have been reported for our surgical colleagues as well. Clearly, education of health care providers on optimal transfusion practices remains a knowledge gap and an essential element of PBM programs.[44]

Patient Blood Management For the Optimization of Transfusion Practice

Definitions

AABB: Patient blood management is an evidence-based, multidisciplinary approach to optimizing the care of patients who might need transfusion. PBM encompasses all aspects of patient evaluation and clinical management surrounding the transfusion decision-making process, including the application of appropriate indications, as well as minimization of blood loss and optimization of patient red cell mass.[45]

Society for the Advancement of Blood Management (SABM): PBM is the timely application of evidence-based medical and surgical concepts designed to maintain hemoglobin concentration, optimize hemostasis and minimize blood loss in an effort to improve patient outcome.[46]

Pillars of Patient Blood Management

Perioperative PBM generally focuses on three pillars of care in surgical patients: the detection and treatment of hematologic derangements (e.g., anemia, thrombocytopenia, or coagulopathy); reduction of perioperative blood loss; and harnessing and optimizing the patient-specific physiological reserve of anemia, thrombocytopenia, and coagulopathy (including restrictive transfusion triggers and use of pharmacologic hematologic adjuncts such as Prothrombin Complex Concentrates when appropriate).[47-49]

Pillars of a Patient Blood Management Program

Clinical champions and institutional 'buy-in': A key element with most all of health care's change management initiatives is the identification of a clinical champion who can lead the effort. This individual will serve many key roles in the PBM process as they must convince institutional leadership of the importance of the effort while 'selling' PBM as the approach to address the problem. This initial effort should not be under-appreciated as it is required to garner the resources needed for the success of the PBM program. The clinical champion will also oversee the interactions with the clinical practice. Effective leaders must be skilled in many areas including business acumen (vision, strategic planning, human resource management), change management (project management,

problem solving, decision making), interpersonal skills (communication, team building, negotiations), and health care leadership (operational excellence, health care policy, health care quality).[50]

Organizational structure: Implementation of a PBM program must take into account the key stakeholders. Success depends on a robust PBM 'team' inclusive of members who represent the clinical service lines that will be impacted by PBM-related interventions. Examples of key stakeholders include: Emergency Medicine, Internal Medicine/Family Practice, Surgery (e.g., Cardiothoracic, Trauma, and Orthopedic), Anesthesiology, Critical Care Medicine, Hematology/Oncology, Transplantation, Transfusion Medicine, Pediatrics, and Nursing. Additional stakeholders also include administrative partners and Information Technology personnel. These participants will have unique and essential perspectives on the 'culture' of the environments that they represent. Changes to clinical workflows are often better accepted when the rationale is delivered by a respected colleague. These key stakeholders can also greatly facilitate the dissemination of best practices guidelines, performance metrics, and quality concerns.

Data-driven approach to understanding transfusion practices: Health care providers often have perceptions regarding their clinical practice. However, when valid clinical data are available, it often contradicts these clinical impressions. As with so many other areas of health care, data-driven approaches to understanding the transfusion landscape can prove impactful.[51] Moreover, data detailing the impact of specific PBM interventions can add significant value to a PBM program. Recently, Crohn and colleagues have shown a data-driven approach to PBM can markedly reduce the proportion of inappropriate transfusion orders and the number of overall transfusion events.[52] Whenever possible, data detailing the transfusion practice, adherence to best practice guidelines, and occurrence of adverse events should be made available to help guide the PBM program.

Defining and disseminating best practices: Having developed and implemented the necessary infrastructure to support a PBM program (e.g., people, processes, technology), a key early PBM activity is the development of best-practice guidelines that can be disseminated to the clinical practice. In addition to best-practice guidelines for pre-operative evaluation/optimization and use of blood components therapies, consideration of strategies that can minimize perioperative blood loss and reduce the risk of exposure to allogeneic blood products should be considered. Examples of evidence-based intraoperative interventions include point-of-care testing and pharmacologic interventions (e.g. anti-fibrinolytic therapies, prothrombin complex concentrates, topical hemostatics) as well as additional strategies such as acute normovolemic hemodilution, and intraoperative autologous red blood cell recovery.[16] These strategies should be specifically considered in patient at high risk for excessive bleeding (e.g., major cardiac, orthopedic, thoracic, or liver surgery). Information related to the risks of blood transfusion as well as the economic implications of liberal transfusion practices should also be disseminated broadly.

Optimizing clinical decision support and implementing innovative informatics approaches: When evaluating the individual components of a PBM program, implementation of well-thought electronic clinical decision support (CDS) tools have been shown to meaningfully impact transfusion behaviors. CDS implemented at the time of order entry can assist clinicians by helping to guide them towards appropriate transfusion behaviors or alternatively steering them away from the administration of blood components when potential recipients are unlikely to benefit. Even apparently simple interventions such as defaulting the transfusion 'dose' to a single unit of RBC, as opposed to multiple units, can have very meaningful impacts on overall transfusion practice.[53] A recent systematic review highlighted the impact of electronic decision support on transfusion practice.[54] Although the Mayo Clinic transfusion practice has noted a significant impact with the meaningful implementation of CDS for all of the major transfusable blood components, the published evidence in support of non-RBC blood components is less robust than it is with RBC transfusions.[54,55]

Operationalizing performance metrics and quality indicators: Generally speaking, clinicians are competitive individuals who continually strive to outperform. This competitive nature can be leveraged to support meaningful change in transfusion practice. To this end, data can be a powerful driver of change. Indeed, multiples studies have highlighted the importance of providing data back to the practice on how they are performing in terms of optimizing transfusion practices.[52] As with the CDS approaches outlined above, delivery of meaningful transfusion performance metrics or quality indicators to the clinical service-lines appears to be a very key element to optimizing transfusion practice.

Relating the intervention to patient-important outcomes: Ultimately, health care personnel strive to provide the best outcomes possible for their patients. As such, an essential final component for PBM programs is the development of

strategies which tie changes in transfusion practice back to patient-important outcomes. Though seemingly straightforward, linking PBM activities to clinically relevant outcomes can be challenging and remains underdeveloped in most PBM programs. Key steps as we move forward include identifying the relevant outcomes to assess as well as the appropriate methods for their measurement. Candidate outcomes include mortality, morbidity, level and duration of care, and resource utilization.[56] Notably, multiple groups are currently working to further identify key outcomes to be assessed in this domain. Encouragingly, recent work suggests that PBM not only reduces blood product utilization with associated cost savings, but indeed is also associated with improved patient outcomes.[48,49]

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The Quick and Dirty on Anesthesia Care for the Complex Geriatric Patient

Name **City/State**
Shamsuddin Akhtar, M.D.. New Haven, CT
Marek Brzezinski, M.D. Ph.D. San Francisco/California

The Quick and Dirty on Anesthesia Care for the Complex Geriatric Patient

The geriatric patient can be challenging to care for given the high prevalence of complex medical issues, polypharmacy, multiple risk factors, etc. This summary provides a pragmatic and clinician-based approach to anesthesia care in a high-risk, complex geriatric patient. Part I focuses on cardiac challenges with particular emphasis on medications, monitoring, preventative and therapeutic interventions. Part II focuses on other organ systems, including postoperative renal dysfunction and fluid management, as well as postoperative challenges.

I. Cardiac Anesthetic Care for the Complex Geriatric Patient (Shamsuddin Akhtar, M.D.)

Anesthetizing geriatric patients is not a new challenge. One of the earliest lectures on geriatric anesthesia was delivered back in 1957. Fortunately, the expected average survival age was < 65 years and anybody who was > 65 yrs old was considered really old. This has now changed, the expected survival in 2017 is around 80 years. Intraoperative hemodynamics is closely related to baseline cardiovascular function which is affected by aging and comorbidities. It is further affected by anesthetic dozing, respiratory and fluid management.

1. Cardiovascular changes with aging

It is difficult to clearly differentiate the aging process from age-related diseases. In a particular patient, both processes interact to yield the specific physiological state of the system. The general morphologic changes induced in both the vasculature and the heart are similar: with stiffening, thickening, dilatation or enlargement, and endothelial or myocardial dysfunction as common themes. The vascular system is closely coupled to the ventricles and the progressive changes in the vasculature lead to compensatory changes in the cardiac function. The cardiac conduction system and the cardiac valves also degenerate over time. Furthermore, changes occur in the autonomic regulation and the neuroendocrine system, with aging, and impact the cardiovascular system.

a. Cardiac and Vascular morphologic changes with Aging

As the human body ages, there is the increased stiffness of the heart and vascular tree. Vascular stiffness is the result of increased collagen, decreased elastin, glycosylation of proteins, free radical damage, calcification and chronic mechanical stress [also described as ‘fatigue failure’). Aging can radically transform the endothelial layers via changes in extracellular matrix compositions. Furthermore, increase in endothelin-1, vasoconstrictor prostaglandins and decrease and vasodilator mediators lead to vasoconstrictive milieu contributing to atherosclerosis and arteriosclerosis. Atherosclerosis and arteriosclerosis are inflammatory processes. Increased levels of C-reactive protein and increases in erythrocyte sedimentation rate suggest an increased inflammatory propensity in the elderly.10 Some have coined the condition as “inflammaging”, and the process is thought to be due to up-regulation of a range of pro-inflammatory cytokines.

b. Ventricular vascular coupling, diastolic and systolic dysfunction

The above mechanisms serve to explain the pathogenesis of vascular stiffness associated with aging. As the heart is closely coupled to the vascular system, it is important to note that many of the changes to the aging heart are closely linked to progressive changes in the vascular system. The vascular system serves both as a reservoir and a conductive system. It serves a critical role in buffering the effects of intermittent ejection (stroke volume). In a young person, the aorta and proximal arteries expand 10% with each contraction, whereas the distal muscular arteries expand only 3%.

As arterial walls stiffen, blood vessel compliance is reduced, leading to an increase in systolic blood pressure and pulse wave velocity. The reflected waves return earlier to the thoracic aorta, arriving by late ejection instead of early diastole. Thus, the left ventricle must pump against a higher pressure in late ejection than under normal circumstances. This additional afterload places an increased burden on the heart, particularly because it occurs late in systole when the myocardial muscle is normally losing its strength, and therefore provides a significant stimulus for cardiac hypertrophy.

The cardiac muscle hypertrophy that develops secondary to the increased late systolic afterload also leads to myocardial stiffening and diastolic dysfunction. Diastolic dysfunction is defined as impairment in the relaxation phase of the ventricles. As a consequence, there is a progressive decrease in the early diastolic filling period between the ages of 20 and 80. At its worst, the diastolic filling period is reduced by 50% compared with younger controls. Because the passive early ventricular filling is impaired with age, the heart is increasingly dependent on an adequate atrial filling pressure and the atrial contraction. The atrial pressures must rise to maintain the end-diastolic volume in the presence of stiffened ventricles. The increased atrial pressure can result in increased pulmonary blood pressures and ultimately lead to congestion in the systemic venous circulation. The cumulative effect of these alterations results in diastolic dysfunction.

Systolic function of the heart also is affected by the aging process. From a functional standpoint, the prolonged myocardial contraction maintains the flow delivered to the stiffened arterial tree, thereby maintaining cardiac output. The functional adaptation to vascular stiffening and afterload is able to maintain cardiac output at rest; however, an age-related decline in systolic function may be unmasked in the presence of exercise or sympathetic stimulation.

Reduced vascular compliance, diastolic dysfunction, and systolic dysfunction in the elderly are all interconnected. It is reasonable to assume that these are not separate pathologies and in fact develop in parallel. Reduced vascular compliance resulting in hypertension, increased afterload, and eventual cardiac remodeling is an extremely common finding in the aging population. In a large portion of this group, this inevitably results in some evidence of diastolic dysfunction. Furthermore, the above concepts demonstrate that some systolic dysfunction exists in many of these same hypertensive elderly patients.

c. Increased pulse pressure and risk of MACE

Generalized stiffening of the arterial tree leads to increased arterial wave reflectance, increased systolic blood pressure, decreased diastolic blood pressure and a widened pulse pressure. Widened pulse pressure is a hallmark of aging and has been associated with poor clinical outcomes. High systolic and low diastolic pressure also predispose the elderly patients to myocardial ischemia. Because of the consequences of arterial stiffening, arterial compliance has been suggested as a better measure of biologic age, as opposed to chronologic age.

d. Neuro-endocrine changes with aging that affect the cardiovascular system

Aging of the neuro-endocrine system can have a significant effect on the cardiovascular system. Changes include the number of adrenergic receptors in the cardiac and vascular tissues, attenuation of signal transduction pathways, and changes in the balance between sympathetic and parasympathetic activity. The renin-angiotensin-aldosterone system, vasopressin and natriuretic peptides are also affected by aging.

2. Anesthetics and Aging

Elderly patients are very sensitive to anesthetics. Volatile agents are direct vasodilators and are known to depress baroreflex responses. Furthermore, volatile anesthetics can produce myocardial depression and nodal rhythms that are poorly tolerated in patients with cardiac abnormalities such as aortic stenosis, mitral stenosis, or hypertrophic obstructive cardiomyopathy. A preference might be given to less soluble, volatile anesthetics because they can be titrated up or down quickly, and emergence times as well as time to orientation are remarkably better than with the older volatile anesthetics. Maintenance can include nitrous oxide when appropriate, because it helps to maintain sympathetic outflow and lessens the need for higher concentrations of the potent volatile anesthetics. Importantly the MAC of volatile anesthetics decrease by 6-8% per decade after 40 yrs and end-tidal concentrations should be adjusted downward. Unfortunately, this is rarely achieved in contemporary practice.

Intravenous anesthetics have a more pronounced hemodynamic effect, with smaller doses being required to achieve the same anesthetic level. This is due to pharmacokinetic and pharmacodynamic changes in the elderly. The dose of induction agents should be decreased by 25 - 50%. Adjusting the anesthetic dose for patient age may help reduce unnecessarily deep anaesthesia, associated hypotension and potentially reduce adverse outcomes.

Additionally, adequate analgesia is an important aspect of heart rate and blood pressure control, but dosage of opioids should be adjusted for age. Benzodiazepines should be minimized or avoided because they interact with opioids to produce sympatho-inhibition and hypotension and can be associated with post-operative delirium.

Neuromuscular blockade should be used judiciously in the elderly with close neuromuscular blockade monitoring. Residual neuromuscular blockade can have disastrous consequences and lead to pulmonary complications.

3. Management of intraoperative cardiovascular instability

a. Adjust anesthetic dose: In the presence of muscle relaxation, the amount of anesthetic required to achieve amnestic/unconscious state is 33 -50% of the age-adjusted MAC. So, anesthetic doses can be decreased significantly.

b. Adjust ventilator settings: Decrease tidal volume (6-8 ml/kg) , administer PEEP (6-8 mmHg).

c. Vasopressors: In all but the sickest of older patients, the most likely mechanism of intraoperative hypotension is either decreased vascular resistance or hypovolemia. Bradycardia could be involved but is easily detected and treated. Vasopressors are to be considered in managing the hypotensive patient even after adequate volume deficits are replaced and both ephedrine and phenylephrine are the most frequently used drugs. Phenylephrine has the advantage over ephedrine in that it does not exhibit tachyphylaxis and will not promote tachycardia that is unwanted in diastolic dysfunction. Furthermore, α-receptor activation promotes venoconstriction in addition to vasoconstriction, thereby shifting blood from the periphery back to the heart and alleviating the anesthetic-induced peripheral pooling. As with all drugs, adverse consequences can occur. Coronary vasoconstriction, decreased cardiac output, imbalance in the distribution of the cardiac output, and wall motion abnormalities are all potential undesired effects. The key to the rational use of pressors such as phenylephrine is to lessen hypotension, while not striving to increase vascular tone back to preanesthetic levels. In other words, tolerate a mild decrease in blood pressure.

The cardiac side-effects that have been observed with the phenylephrine typically associated with elevated blood pressure above the patient's normal state, or under unusual cardiac loading conditions such as deep anesthesia.

Hypertension and tachycardia should be recognized as undesirable events in the elderly because of the increased myocardial oxygen demand and the reduced time for atrial filling and coronary flow. Esmolol is useful (0.5–1.0 mg/kg) to attenuate the intubation response and avoid excessive increases in heart rate. α2-Agonists such as dexmedetomidine also are effective in reducing the sympathetic response to laryngoscopy and intubation, but add to intraoperative hypotension.

d. Administer fluids judiciously: One of the primary goals of fluid therapy is to achieve adequate cardiac index/stroke volume, for a particular clinical situation, by maintaining optimal preload. In the perioperative setting, one of the biggest challenges has been to determine accurately (and easily) the fluid status of the patient. Static markers of preload (central venous pressure, pulmonary artery wedge pressure, etc.) have been used for decades and are still used to guide fluid therapy. However, these markers are not very accurate. Non-invasive, dynamic indices like pulse pressure variation (PPV), systolic pressure variation (SPV) and stroke volume variation (SVV) may be better predictors of volume status. Though the British guidelines recommend using flow directed monitors to determine fluid status, one should keep in mind that most of these studies are small and results may not be applicable to elderly patients. Thus, even though the "best" method to manage fluids in the elderly is unclear, it is clear that a keen sense of pathophysiology, effects of anesthetic drugs on CV function and attention to volume losses will promote a good outcome.

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II. Beyond the Heart: Perioperative Care of the Complex Geriatric Patient (Marek Brzezinski, MD PhD)

With growing geriatric population in the US, an increased emphasis has been placed on anesthesia care for the elderly.[1-5] Geriatric care is quickly becoming a key area where Anesthesiologists can have a major positive impact in the overall patient experience including their physiologic and emotional well being which can translate into better clinical outcomes and increased satisfaction.[3] To accomplish these goals, the Anesthesiologist needs to be familiar with the potential and unique considerations in the elderly patient, as well as understand the key issues and main complications in this medically complex patient population.[3] The interested reader is referred to the best practices, entitled *"Optimal Perioperative Management of the Geriatric Patient",* providing guidance on managing the older adult in the perioperative period (https://www.facs.org/quality-programs/acs-nsqip/geriatric-periop-guideline).[1] The overall goal of the anesthesia care can be summarized as:

- ***Keep the elderly patient mentally and physically active*** *(i.e. less sedation, multimodal pain control) to prevent complications (e.g. DVT, infections, functional deconditioning, cognitive problems) as well as* ***normothermic***
- ***Avoid both extremes of intravascular volume (hypo-/hypervolemia)***
- ***Prevent N/V and ileus*** *to facilitate their recovery and wound healing,* ***while***
- ***being cognizant of reduced renal/hepatic function and*** *the prevalent* ***polypharmacy.***
  - ***Multidisciplinary approach*** *is the way to do it!* ***[1, 2, 5]***

1.0 Unique considerations relevant for postoperative care in the elderly patient[1, 2, 5, 6]

Aging affects baseline physiological functions, as well as the response to stressors and medications. Consequently, it is essential for the clinician taking care of geriatric patients to be familiar with those changes:

- Pharmacokinetic and pharmacodynamic changes in the elderly.
  - Aging is typically associated with an increase in adipose tissue mass accompanied by a loss of skeletal muscle mass, lean body mass, and total body water; decrease in renal and hepatic function (see below), as well as malnutrition (low albumin). Consequently, the geriatric patient has
    - Increased reservoir, protracted clearance, and an increased duration/effect of lipid-soluble medications (e.g., opioids and benzodiazepines)
    - Decreased reservoir for albumin-bound drugs, like diazepam or propofol, potentially leading to high plasma concentration of the free drug.
    - Decreased volume of distribution, and therefore higher plasma concentrations and greater clinical effects of water-soluble drugs
  - Consequently, the elderly patients frequently require a reduction in the dose of their medications.
- Polypharmacy is highly prevalent, with 40% taking ≥ 5 medications and 20% taking ≥ 10 medications per week.
- Kidney function decreases throughout life. In fact, the clinician should assume a 30-50% reduction in GFR in a geriatric patient. The elderly surgical patient has a higher risk of electrolyte and fluid shifts as well as of acute renal failure after surgery.
- Liver function in the elderly is decreased, leading to an overall decrease in metabolism and clearance of medications commonly used by the anesthesiologist.
- Aging brain can be associated with a decline in cognition as well as an increase in drug-sensitivity. Furthermore, the respiratory drive is decreased, as is the autonomic response to hypoxia and hypercapnea (by 40-50%). Consequently, the elderly patient is more sensitive to sedatives (e.g., 2x higher sensitivity/risk of respiratory depression).
- The GI tract undergoes significant changes as we age. For one, the gastric drug absorption is delayed, i.e., there is an inconsistent dose-(time-)response relationship. The elderly patient has a higher risk of aspiration, as swallowing dysfunction and the loss of the coughing reflex is commonly reported in this population; up to 30% carry the diagnosis of GERD. Gastric atrophy is also prevalent, thus increasing the risk of GI bleed. Finally, up to 30% of the geriatric population takes laxatives preoperatively for chronic constipation.
- Co-morbidities are prevalent in the elderly. They frequently have COPD, CAD, heart failure, diabetes, etc., placing them at higher risk for perioperative morbidity and mortality.

2.0 Postoperative Renal Dysfunction[7, 8]

Acute kidney injury (AKI) in geriatric patients undergoing non-cardiac surgery has been reported to be more than twice as prevalent as in general population (20% vs. 8%, respectively).[9-11] In addition of being at higher risk for developing AKI, the geriatric patient has also a reduced capacity to recover from such injury.[7, 8] The clinical significance of AKI arises from its association with increased morbidity and mortality, including higher risk for development of chronic renal disease.[12, 13] The

underlying mechanisms leading to AKI in non-cardiac surgery are commonly multifactorial, and include inflammatory mediators, ischemia-reperfusion, and poor microcirculation in the context of already existing age-related renal changes.[7, 14] The identified risk factors of AKI include older age, obesity, CHF, PVD, liver disease, and alcohol abuse.[15] There is considerable controversy in the literature about the best approach to prevent postoperative renal dysfunction. And while many different strategies and medications have been suggested, the evidence for most of them is limited and inconsistent.

- Anti-inflammatory medications:
  - Aspirin. Observational studies reported an up to 60%-reduction of AKI with aspirin. [16, 17]
  - Statins have been studied due to their anti-inflammatory effects, with the majority of studies failing to identify reno-protective effects.[18-20]
- Vasoactive drugs
  - Dopamine. It is now well-established that dopamine does not prevent AKI.[21, 22]
  - Fenoldopam. Despite few encouraging early studies, a recent randomized clinical trial failed to identify any benefit of this selective dopamine-1 receptor agonist on the incidence of AKI. [23]
- Renal vasodilators
  - Atrial natriuretic peptide (ANP) emerged recently as a very promising prophylactic intervention, with multiple clinical studies in different surgical populations demonstrating renoprotective effects and a decreased incidence of AKI.[24-26]
- Remote ischemic preconditioning continues to remain an enigma with studies providing conflicting data: on one side there are several well-designed and powered studies published in high impact journals, e.g. NEJM, that failed to demonstrate any benefit, while other well-designed studies published in other high impact journals, e.g. Anesthesiology, demonstrated a clear short-and long-term benefit.[27-29] Time will tell.

Of note, in patients with postoperative renal dysfunction who require analgesia the clinician should: [30, 31]

- Not use codeine and meperidine,
- Perform dose adjustments when using morphine (active metabolites accumulate in renal failure), oxycodone (80% metabolized in the liver, 20% excreted unchanged in the urine), or hydromorphone (metabolized in liver, but 3-glucuronide metabolite can accumulate and produce neuroexcitatory effects)
- Use Fentanyl, as it seems to be safe in renal impairment

3.0 Fluid management

The statement by Spahn and Chassot from 2005 is more valid than ever: *"Only combining monitoring with a clear management algorithm aiming at optimization of the stroke volume with colloid boluses in the presence of a knowledgeable anesthesiologist will improve the outcome of patients with concomitant cardiac disease undergoing noncardiac surgery."[33]*

Despite a significant body of literature, the question on the appropriate strategy to perioperative fluid management remains largely unanswered. What we know however, is that the extremes of intravascular volume (hypo-/hypervolemia) should be avoided: One can lead to hypoperfusion, the other to venous congestion, intra-abdominal hypertension, and tissue edema – both extremes are known to negatively impact renal function.[7, 8] Fluid overload should be avoided in patients with diastolic dysfunction. Hypovolemia (absolute or relative) and hypotension should be avoided given impaired renal autoregulation in the geriatric patient.[32]

Particularly frustrating and confusing for the clinician is the fact that fluid restriction as well as volume expansion has been shown to both improve and worsen outcome.[7, 8, 33] Furthermore, the literature on goal-directed therapy (GDT) is inconsistent, with early studies strongly supporting the use of GDT (often small and single-center studies), and the more recent literature (meta-analyses, larger prospective trials, multi-center) failing to demonstrate any benefit of GDT.[33-39] This being said, elderly, high-risk patients undergoing major surgery have been consistently found to represent the group benefitting the most from GDT. Finally, GDT literature suggests that colloids may provide volume expansion without negative fluid overload effects, such as intestinal edema.[33]

Low blood pressure should be avoided. And while there is no consistent definition of what actually constitutes "low BP", a recent study by Walsh et al. demonstrated that even 5-minute time period spent below MAP of 55 mmHg was independently associated with an 18% increased AKI risk. [11]

Finally, hydroxyethyl starch and 0.9% NS solutions have been reported to increase the risk for development of AKI.[40, 41]

4.0 Postoperative Complications in the Elderly Patient

Given the page-limit, the RCL-synopsis here focuses on two postoperative complications that received increased attention recently:

- **Postoperative cognitive decline** is a common complication that can present as two separate entities:

- **Postoperative delirium (POD):** an acute, early-onset, and transient disturbance of consciousness that is characterized by inattentiveness and cognitive impairment which has a fluctuating course.[42] POD is one of the most common complications in the elderly surgical patient. Clinically, POD can present in three different subtypes: hyperactive delirium (i.e., the "prototypical" combative and agitated delirious patient), hypoactive delirium (calm and quiet patient with decreased motor activity), and mixed subtype.[1] Typically, POD is diagnosed using the Confusion Assessment Method for the ICU (CAM-ICU) [for ICU patients] or Confusion Assessment Method (CAM) [for ward patients]. The reported incidence of postoperative delirium ranges from 5% to 15%, with rates as high as 16% to 62% in high-risk groups, such as hip fracture patients.[1, 43] Multiple risk factors for development of postoperative delirium have been identified, with preexisting cognitive impairment and advanced age being the strongest predictors of postoperative delirium.[1, 44] Development of delirium is associated with increased mortality,[44] increased risk of institutionalization,[45] development of dementia,[45] increased length of stay,[44] as well as with increased risk of major complications.[44] The occurrence of delirium can predict long-term cognitive impairment.[45]
  - Prevention: According to recent Cochrane reviews,[46, 47] 30-40% of cases of delirium are preventable using multi-component interventions, including individualized care, pain management, cognitive reorientation, daily mobilization/activity, attention to sensory deprivation, constipation prevention, facilitation of sleep, geriatric-focused training of staff, etc.
  - Treatment:[1] It is currently recommended to start with the above mentioned multicomponent non-pharmacological interventions. Though the data on the role of antipsychotic drugs in prevention of postoperative delirium are too limited to draw any firm conclusion, an antipsychotic agent like haloperidol starting at 0.5-1mg PO commonly represents the second step in treatment of PD. There is no clear evidence that melatonin or melatonin agonists reduce delirium incidence compared to placebo.[47]
- **Postoperative cognitive dysfunction (POCD):** a longer-lasting decline in the level of cognitive performance after surgery as compared to preoperative baseline.[48] It includes acute (weeks), intermediate (months), and long-term (years) cognitive decline. Up to 50% of surgical patients suffer from POCD in the early weeks following a major non-cardiac surgery.[49] Although the majority of patients gradually recover over time, permanent cognitive decline has been described.[50]Advanced age, history of cerebral vascular accident, lower educational level, and alcohol abuse have been shown to be independent risk factors for POCD at 3 months.[49] POCD was found to be associated with poor short-term and long-term outcomes including depression, decrease in daily functional ability, loss of independence, premature unemployment, and possible permanent dementia.[51, 52] Here are few clinically relevant pearls:[53]
  - There is currently no strong evidence in humans that anesthetic agents or anesthetic techniques are a risk factor for POCD.[54-56] Two meta-analyses that compared GA vs. RA failed to demonstrate that GA is a risk factor for POCD.[57, 58] In two recent clinical trials, the incidence of POCD in patients undergoing an intervention under RA or MAC was at least as high as in the GA group.[54, 59]
  - Furthermore, while volatile anesthetics have been found to promote and accelerate AD-neuropathology in animal models, all human studies examining this subject have failed thus far to show such a relationship.[60-62]
  - The mechanism underlying POCD is unknown.
  - Prevention/treatment: Currently there no prophylactic/therapeutic interventions that consistently and predictably reduce the incidence of POCD.

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Anesthetic Management of Patients Undergoing Spine Surgery

Susan Black, MS **Birmingham, AL**

Patients undergoing surgical procedures of the spine represent a diverse group of patients with varying severities of pathology, undergoing a wide range of procedures from minimally invasive to high-risk multilevel procedures. Developing a perioperative management strategy to optimize outcome for these patients requires understanding of the disease processes, surgical procedures, and options for management.

Airway Management

Patients with cervical spine pathology require special consideration for airway management. Patients with cervical spine disease have a higher incidence of difficult intubation, in particular those with rheumatoid disease, cervical fractures or tumors, disease involving the upper cervical spine, and with internal or external fixation. In patients with cervical spine disease conventional airway assessment remains the best predictor of encountering a difficult airway. Cervical spine pathology in patients with a concerning airway exam further increases the potential for difficulty.1 Endotracheal intubation in the presence of cervical spine disease may be associated with risk of neurologic injury. In patients with an unstable cervical spine, intubation is not associated with an increased risk of neurologic deterioration compared to those not requiring intubation (1-2%) if the instability is recognized.2 In patients with unrecognized cervical spine instability, risk of neurologic deterioration with intubation is significantly increased to approximately 10%.3

Studies have attempted to identify optimal techniques for intubation in patients at risk for cervical spine injury.4 During airway maneuvers, the greatest motion of the cervical spine has been shown to occur at the atlanto-occipital junction followed by the junction of the first two cervical vertebrae.5 In patients with known or suspected cervical spine instability it is important to limit motion of the cervical spine during airway management. Use of manual in line stabilization remains the most accepted technique to limit motion, but is associated with increased difficulty in obtaining an optimal view of the glottic opening. A wide variety of intubation techniques have been evaluated for use in these patients. Direct laryngoscopy is the tool with the longest history of documented safe use. A number of devices including indirect laryngoscopes, laryngeal mask airways, and fiberoptic scopes have been shown to be effective in limiting motion of the cervical spine while managing the airway. Depending on the clinical situation including airway examination, patient's mental status and other comorbidities, and experience of provider, one of these techniques may be advantageous. In planning airway management of patients undergoing cervical spine surgery awareness of the risk of spinal cord injury with intubation, recognition of the increased risk of encountering a difficult airway, and attention to minimizing motion of the cervical spine are more important to success than choice of a particular technique.

Certain patient groups may also have risk of postoperative airway problems – the difficult extubation patient. Patients undergoing multiple level anterior cervical spine procedures may be at risk for postoperative neck and airway edema causing airway compromise with airway complications occurring in up to 6%, requiring reintubation in approximately 2%, and leading to mortality in 0.3%. Identified risk factors are operative time > 10 hours, requirement for > 4 units transfusion, obesity, reoperations, and operations of 4 or more cervical spine levels or involving the second cervical vertebrae.6 Authors of a recent review article divided risk factors into primary or surgical factors, and secondary either patient or anesthetic factors. Based on their review they recommended that patients be classified as high risk (>1 surgical risk factor), intermediate risk (1 surgical risk factor) and low risk (0 surgical risk factors). High-risk patients should be left intubated until surgical edema resolved. Intermediate risk patients require assessment of secondary factors. Intermediate risk patients with one or more secondary factors may warrant delayed extubation while intermediate risk patients without secondary factors could be extubated immediately postoperatively but have more intensive monitoring in the first 12 to 24 hours postoperatively. Low risk patients require no special consideration for extubation.7

Table 1: Risk Factors for Delayed or Failed Extubation

Primary factors	Secondary factors	
Surgical	Patient	Anesthetic
Duration > 5 hours	Morbid obesity	Grade 3-4 view
> 3 levels	Pulmonary disease	Multiple intubation attempts
C2-C4	Cervical myelopathy	Fluids
> 300 EBL	Prior c-spine surgery	
Anterior + posterior		

Hemodynamic Management

In some circumstances induced hypertension is utilized in spine procedures, particularly in cervical spine procedures in patients with significant cord compression. It is a common practice to maintain very strict control of blood pressure intraoperatively utilizing direct arterial pressure monitoring and attempting to maintain systemic perfusion pressure at or very near awake levels. While this has not been studied in a prospective fashion, it is believed by many neurosurgeons and neuroanesthesiologists to be important in minimizing risk for new neurologic injury in this patient population. 8 On the other hand, induced hypotension continues to be utilized in some centers for patients undergoing procedures associated with high perioperative blood loss, in particular multilevel thoracic and lumbar reconstructive procedures. There is little evidence to indicate that mild degrees of induced hypotension as is most commonly utilized in these procedures is effective to significantly decrease perioperative estimated blood loss or perioperative transfusion requirement. However, less bleeding in the operative field, may improve surgical exposure. This may be an appropriate and effective strategy in patients that are not placed at increased risk of perioperative morbidity by the use of mild degrees of induced hypotension.9

Transfusion Management

While many surgical procedures of the spine are not associated with large blood loss, procedures involving significant bone work at multiple levels may be associated with large intraoperative blood loss and a high incidence of transfusion. A number of factors have been found to predict requirement for transfusion allowing us to identify patients at risk for high blood loss who would benefit by interventions that decrease need for transfusion. 9-13 Of note, recent studies have reviewed the impact of antiplatelet medications.14-16 Use of clopidogrel with proper discontinuation preoperatively was found to be associated with a higher estimated blood loss, but no difference in need for transfusion during spine surgery compared to patients never on clopidogrel. Studies investigating the impact of aspirin have found that patients chronically on aspirin have a higher blood loss but no difference in transfusion requirement independent of whether the aspirin is continued or discontinued preoperatively. For patients on aspirin following cardiac stent placement, these results suggest that aspirin should not be discontinued routinely prior to spine surgery. Aspirin will not impact transfusion requirement and discontinuation could be associated with an increased thromboembolic complication risk.

Table 2: Factors predicting need for perioperative transfusion during spine surgery			
Patient Factors		Procedure Factors	
ASA Classification	>3 associate with higher loss	Location	Lumbar & thoracic > cervical
Gender	Female > male	Number levels	
Age		Fusion	
Weight loss		Complexity	
Preoperative Hg		Surgeon specialty	Orthopedics > neurosurgery
Coagulopathy			
Coumadin use	Even if lab normal		

Several techniques to decrease intraoperative blood loss have been investigated. Induced hypotension is applied most commonly to multiple level thoracic or lumbar spine procedures in healthy patients without neurologic deficits. Efficacy in decreasing blood loss and transfusion has not been consistently demonstrated.17 Operative positions which prevent abdominal compression (such as the Jackson table) have been reported to result in less blood loss as compared to positions in which some degree of abdominal compression may occur (prone on bolsters or Wilson frame). Antifibrinolytic agents, tranexamic acid and aminocaproic acid, have been shown in many studies to decrease intraoperative and total perioperative blood loss with some studies demonstrating a decrease in transfusion of blood products and others revealing no difference in transfusion requirements. Use of these agents has not been associated with complications related to hypercoagulation.10,17,18 In a small series, recombinant activated factor VII was shown to be effective at decreasing intraoperative blood loss and transfusion in patients undergoing multiple level spinal fusion procedures when given after loss of 10% of estimated blood volume.19 However this practice has not been studied in a large population.

Numerous approaches to decrease requirement for homologous blood transfusion have also been investigated. Epoetin alfa administration preoperatively has been shown to decrease requirement for homologous transfusion in some studies, either alone or in combination with preoperative autologous donation, but has been was associated with a higher incidence of deep venous thrombosis when pharmacologic antithrombotic prophylaxis was not used.20,21 Preoperative donation of autologous blood, immediate preoperative hemodilution and collection of autologous blood, and perioperative blood salvage have all been utilized in spine surgery to decrease requirement for

intraoperative homologous transfusion. Each has been shown to be similarly effective used alone, but in most circumstances combination of more than one of these techniques does not further decrease requirement for homologous blood products.22-24 In addition, numerous recent studies have pointed out the high rate of wasting of autologous units collected prior to spine surgery with wasting of at least one unit in up to 50% of patients undergoing scoliosis correction.25 A meta analysis reviewing available maneuvers to decrease transfusion found that there was good evidence to support the use of antifibrinolytic agents, while there was little of no evidence to support recombinant factor VII, induced hypotension, staging of long procedures, normovolemic hemodilution, or intraoperative cell salvage. To decrease requirement for transfusion during spine surgery and the associated complications, it is important to first identify the subset of patients at risk for large blood loss and then selectively utilize one of the available techniques with potential to decrease need for homologous transfusion. Patients expected to loose less than 10% of their estimated blood volume will likely not benefit from utilization of the techniques described above, those anticipated to loose 10-30% of estimated blood volume will see benefit from use of one technique, and combination of multiple techniques is only indicated when a very high blood loss is anticipated. In all patients optimal preoperative preparation (i.e. anemia management) and optimal positioning to lessen requirement for transfusion is appropriate. Over the last decade rates of transfusion of blood products during spine surgery have not decreased as they have in other procedure types. Rates of transfusion of allogeneic blood have increased and the use of autologous products has decreased. The reason for this in the face of increasing emphasis on decreasing transfusion of banked blood is unclear.26

Postoperative Pain Management

Spine procedures may be associated with significant postoperative pain. Neuraxial techniques including intrathecal narcotics and postoperative epidural analgesia have been shown to be effective techniques in lumbar and thoracic procedures and are not associated with increased incidence or delayed diagnosis of neurologic injury if the dosing regimen is planned to allow early neurologic assessment. Benefits include earlier return of bowel function, earlier mobilization, shorter hospital stay, improved pain control at rest and with movement, less nausea and vomiting, and less puritis.27,28 Wound catheters with infiltration of local anesthetic have also been effective in pain relief and to decrease the incidence of chronic dysesthesias.29 Multimodal medication regimens including pre and post operative oral controlled release narcotics, perioperative ketamine, preoperative methadone, perioperative oral pregabalin or gabapentin, and scheduled perioperative acetaminophen or nonsteroidal anti-inflammatory agents have been shown to improve pain management and decrease systemic narcotic side effects.30-32 In a prospective study utilizing patient survey postoperatively, a variety of multimodal regimens were compared. There was no difference between medication combinations, however when multimodal regimens were instituted preoperatively they were more effective, resulting in better pain control postoperatively and function after discharge compared to similar regimens initiated postoperatively.33 Multimodal techniques in particular when instituted preoperatively appear to offer advantages over single medication regimens after spine surgery as has been seen in many other procedure types.

Neurologic Monitoring and Injury Prevention

Neurologic monitoring may be utilized in a number of spine procedures. During repair of scoliosis, continuous neurologic monitoring is considered an indicated technique by the Scoliosis Research Society and is felt to result in a lower risk of intraoperative neurologic injury.34 Neurologic monitoring of other spine procedures in patients felt to be at high risk for neurologic injury is felt by some to decrease risk of neurologic injury, but is not utilized consistently in all centers. Somatosensory evoked potential (SSEP) and transcranial motor evoked potential (TcMEP) monitoring are utilized in patients felt to be at risk for spinal cord injury either from surgical trauma, operative position, or impairment of blood supply. Electromyography (EMG) is utilized when it is felt that nerve roots may be at risk during the procedure, most commonly with lumbar stabilization procedures. In a recent single center retrospective study of multimodality intraoperative neurologic monitoring in over 12,000 spine surgeries, the authors reported a low false negative rate of 0.36%, but these injuries were likely to be permanent. In contrast the same group reported a 3% rate of monitoring changes intraoperatively, with only 3.8% of those changes leading to permanent neurologic injury. The authors suggest that while even properly performed monitoring will have a low rate of false negatives, events detected intraoperatively can most often be corrected limiting risk for injury. 35-37 SSEP monitoring places some limitation on anesthetic management, most notably limiting the dose of volatile agents and benzodiazepines. Likewise TcMEP monitoring impacts anesthetic management. Most commonly intravenous techniques are utilized (propofol and/or narcotic infusion with nitrous, benzodiazepines, ketamine, or lose dose volatile agents). Patients' disease states influence ability to successfully monitor their neurologic function intraoperatively. Patients with preexisting neurologic deficits, diabetes mellitus, and hypertension have an increased

rate of inability to monitor MEP's intraoperatively. Having more than one disease or use of volatile anesthetic agents increased the risk of failure to monitor further.37 EMG requires avoidance of muscle relaxants.

Postoperative Vision Loss

Postoperative vision loss is a rare complication of spine surgery occurring in 0 – 0.1% of cases.38-41 While awareness of this complication has increased over the last decade, the incidence nationally appears to be decreasing.42 Postoperative vision loss is most often due to posterior ischemic optic neuropathy (PION), less commonly anterior ischemic optic neuropathy (AION), and rarely due to other reported causes of postoperative vision loss; central retinal artery or vein occlusion and occipital lobe infracts. Reported risk factors for postoperative ION include patient factors such as risk factors for atherosclerotic disease and intraoperative factors. While occasional cases of vision loss due to positioning errors with pressure on the eye are reported, this rarely appears to be a factor. The prone position is associated with significant increases in intraocular pressure and potentially, retrobulbar pressure. Some have postulated that acute venous congestion and a compartment-like syndrome develops in the retrobulbar space predisposing these patients to ischemia of the optic nerve. Both head dependent positioning and vigorous fluid resuscitation could contribute to this phenomenon.43,44 In a recent case control study the Postoperative Visual Loss Study Group investigated factors reported to be with PION.45 Results are shown in Table 3.

Table 3: Proposed Risk Factors Postoperative ION	
Risk factors associated ION	Risk factors not associated with ION
Male sex	Age
Obesity	Comorbid conditions (diabetes, hypertension, smoking)
Use of Wilson frame	Number levels
Anesthetic duration	Head positioning device
Estimated blood loss	Hypotension
Lower colloid use (as % of nonblood infusions)	Lowest HCT
	Vasopressor use
	Total volume, total nonblood volume replacement

Because neither the mechanisms nor definitive risk factors have been identified, methods to prevent this complication are unknown. In fact, the patient profile for those suffering this complication after spine surgery is males aged 45 to 55 with risk factors for vascular disease present in only about 50%. Suggestions for why the incidence has decreased over the last decade despite the fact that the incidence of patient risk factors has increased are related to increased awareness of the complication leading to lower use of the Wilson frame, use of head elevated positions, and subtle changes in fluid and blood pressure management.43 The ASA published a practice advisory in 2006, which was revised in 2012. A summary of the recommendations follows.

- There is a subset of patients undergoing prone spine procedures and receiving general anesthesia that has an increased risk for development of perioperative visual loss, including patients who are anticipated to undergo procedures that are prolonged, have substantial blood loss, or both.
- Consider informing high-risk patients that there is a small, unpredictable risk of perioperative visual loss.
- Blood pressure should be monitored continuously in high-risk patients. Use of deliberate hypotension should be determined on a case by case basis.
- Use of central venous pressure monitoring should be considered in high risk patients. Colloids should be used along with crystalloids to maintain intravascular volume in patients who have substantial blood loss.
- At this time, there is no apparent transfusion threshold that would eliminate the risk of perioperative visual loss related to anemia.
- Use of alpha adrenergic agonists should be determined on a case by case basis.
- High-risk patients should be positioned so that their heads are level with or higher than the heart when possible. In addition, their heads should be maintained in a neutral forward position when possible.
- Consideration should be given to the use of staged spine procedures in high-risk patients.46

Outpatient Spine Surgery

Increasingly, spine procedures are being performed as outpatient procedures. Not only are lumbar procedures commonly outpatient procedures, but in addition cervical spine procedures are being considered as outpatient procedures. Available literature suggests this can be done successfully provided careful patient and procedure selection is carried out. Unplanned admission or readmission is uncommon (2-5%), with no reported complications specifically related to the outpatient status. The most common causes of admission are dural tear,

anesthetic complications, poor pain control, new neurologic symptoms, and urinary retention. In centers with successful outpatient spine surgery practices, common exclusion criteria for outpatient procedures include significant co-morbidities, difficult airway, living a long distance away or living alone, and procedures finishing late in the day. In general postoperative stay is at least 4 to 6 hours to allow detection of the majority of complications. Outpatient spine surgery can be performed safely offering our patients the benefits associated with outpatient procedures including lower cost and lower risk for hospital associated complications.47-49 It will be imperative for anesthesiologists to be involved in the development of protocols for safe outpatient spine surgery, as there is a rapid evolution in practice over recent years. The proportion of more involved cervical spine procedures such as decompressions done as outpatients has doubled in just over a decade, while the number of lumbar disc procedures has increased 5 fold and procedures for lumbar stenosis by nine fold over the same time frame.50

Optimizing Outcome

A number of factors, which can be managed by anesthesiologists in the perioperative period, have been associated with increased risk of complications in retrospective studies. These include presence of anemia preoperatively, operating room delays of greater than 60 minutes, and use of FiO2 less than 50%. 51-53 Postoperative surgical site infections (SSI) after spine surgery cause significant increases in morbidity, hospital length of stay and health care cost. SSI's occur at rate of 0.7 to 4.0 per 100 cases. A number of risk factors have been identified, many of which are not amenable to perioperative intervention and are reflections of the patients disease or co-morbid conditions. These include ASA physical classification, prior spine surgery, operative duration, obesity, and age. However a number of factors can be modified and are under the purview of the anesthesiologist. These include perioperative glucose management, temperature control, and administered FiO2. Patients with nasal colonization by methicillin resistant staphylococcal aureus have been shown to be at a higher risk for SSI, which can be reduced by preoperative treatment with either mupirocin or providone-iodine.54 While as of yet, no large enhanced recovery after surgery (ERAS) protocols have any published results, that work in ongoing. Table 4 indicates the proposed components that have been studied and the impact reported individually for each.55-57

Table 4: Proposed components of spine surgery ERAS protocols

Proposed Component	Impact when studied individually
Preoperative education	Valued by patients
Multimodal analgesia	Improved short & long term outcomes
Minimize blood loss strategies	Proven effective strategies to limit transfusion
Nutrition enhancement perioperatively	Associated with reduced complications
Prehabilitation	Improved outcome when combined with physical therapy postoperatively
Postoperative physical therapy	Advantages of early mobilization

Patients undergoing spine surgery present diverse challenges to the anesthesiologist. Optimal management depends on the anesthesiologist understanding the pathologic process and the risk and needs of the operative procedure. This group of patients is one in which anesthesiologists have the opportunity to significantly improve patient safety and quality of care when we are engaged in the entire perioperative period.

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Ambulatory Anesthesia and Cancer Surgery

Rebecca Twersky, MD, MPH

New York, NY

Introduction

The world of ambulatory anesthesiology is rapidly evolving and changing in order to expand to incorporate more non-traditional ambulatory surgery procedures. This Refresher Course will provide information on the emerging ambulatory surgery oncology procedures and address special considerations and strategies for anesthesiologists to provide safe care focusing on improving short and long term outcomes in this population. Specifically, we will provide information to help develop clinical pathways and enhanced recovery protocols (ERAS) relevant for ambulatory cancer surgery and share available outcomes from an ambulatory cancer surgery center. We will discuss specific pain management strategies and enhanced recovery protocols to shorten length of stay, and improve other important patient outcomes. Finally, we will review clinical evidence of the effects of anesthesia on tumor progression and oncology outcomes and its application to ambulatory anesthesia.

Cancer and Ambulatory Surgery

In 2017, it is estimated that about 1,688,780 new cancer cases will be diagnosed and about 600,920 Americans are expected to die of cancer[1]. Although the overall cancer death rate has dropped in the U.S. and developing countries, despite global advances in prevention, diagnosis and treatment, cancer continues to rank high among causes of major morbidity and mortality. The CDC and International Agency for Research on Cancer[1,2] report cancer as the second leading cause of death in the U.S. and around the globe, accounting for nearly 1 of every 4 deaths. The prevalence increases with age, with 87% of all cancers in the U.S. diagnosed in people $\geq$ 50 years of age or older[1]. With the aging population, it is projected that by 2030, there will be 21.7 million new cancer cases globally and 13 million cancer-related deaths[3]. Since surgery is one of the primary treatments for cancer, it is extremely likely that clinicians practicing in ambulatory surgery will more frequently encounter patients for cancer procedures that may be diagnostic, treatment or palliative procedures in addition to known cancer patients for non-oncology surgery. The challenges of patient selection and geriatric management are compounded with cancer diagnosis. The clear benefits that have emerged over the past four decades of ambulatory surgery providing physical, psychological and economic benefits without compromising the quality of care are becoming more attractive for incentivizing the growth in ambulatory surgery oncology procedures.

Most recent U.S. national statistics reported that in 2010 there were 28.6 million ambulatory surgery visits, which included 48.3 million surgical and nonsurgical procedures; 53% in hospital ambulatory surgery and 47% ASCs[4].The most common ambulatory surgery procedures include, lens and cataract procedures, and other non-invasive surgeries[5]. Ambulatory surgery has increased rapidly due to medical and technological advancements, including improvements in anesthesia and analgesia for pain relief, and the development and shift towards minimally invasive and noninvasive procedures. With this shift to more minimally invasive procedures, surgeons will be doing more cancer related surgery procedures in these outpatient settings. This is also fueled by the growing market of ASCs, currently numbered over 5400.

The contribution of ambulatory surgery cancer related procedures to this growth parallels the increase in prevalence of diagnosis of various tumors and extension of minimally invasive options to oncology surgery. In 2017 is it estimated that there will be approximately 255,188 new cases of invasive breast cancer diagnosed in the U.S.[6]. From 2005 to 2013 the overall mastectomy rate increased 21%[7]. The increasing rates of mastectomy, breast reconstruction and bilateral mastectomies in women with early stage breast cancer were recently reported by Kummerow et al.[8]. They reviewed the trends in breast surgery of over 1.2 million patients from a 14-year period from the National Cancer Database, and found that 57% of women with early stage disease who underwent bilateral mastectomies underwent reconstructive procedures in 2011, compared to the 37% in 1998. Additionally, the proportion of women with nonmetastatic disease who undergo contralateral prophylactic mastectomy (CPM) has increased rapidly, from 5% of total mastectomies in 1998 to 20% in 2011. In 1986, mastectomies were done exclusively as inpatient procedures, by 1995 11% were done in outpatient settings[9] and by 2012, 50% were done as outpatient procedures[7]. Gynecological cancer is the second most prevalent type of cancer among women. In 2016, approximately 60,050 new cases were diagnosed. Surgery, consisting of hysterectomy (often including bilateral salpingo-oophorectomy) without chemotherapy or radiation is used to treat at least 69% of patients with stage I and II disease[10].

Moore et al.,[11] reported on the increase in ambulatory surgeries for hysterectomy and oophorectomy, alone or in combination from 2005-2013. Hysterectomy alone had a 414% increase, or 22.7% increase annually; Oophorectomy had a 35% increase, or a 3.8% increase annually; hysterectomy and oophorectomy combined 276% increase, or an 18% increase annually. Several clinical studies have reported on the feasibility and safety of same-day discharge for these procedures with low readmission rates. Older age, preop lung disease and later surgical end time were risk factors for prolonged stay. Identifying these factors preoperatively could facilitate early discharge[12-15]. Thyroid cancer is the most rapidly increasing cancer in the U.S.[16] and has been increasing world wide of the past few decades[17]. In 2016 it was estimated that approximately 64,300 new cases of thyroid cancer were diagnosed[10]. However, most thyroid cancers are highly curable and the first choice of treatment is surgery[18]. However, the trend toward outpatient surgery has been slower for thyroid surgery, primarily because of the possibility of an expanding hematoma or potentially life-threatening hypocalcemia. A recent study illustrated the postoperative outcomes of total thyroidectomy performed in the inpatient versus outpatient setting in 40,025 patients. The 30-day postoperative complication rate was 7.74% (outpatient, 2.72%; inpatient, 5.02%; $p < 0.0001$). Reintubation, readmission, reoperation and overall complication rates were significantly higher in patients who underwent inpatient total thyroidectomy as compared to outpatients. Patients who underwent outpatient procedures had significantly lower odds of complications[19]. In 2014, 71% of male genital invasive surgical visits (testicular, prostate and penile procedures) were completed on an ambulatory basis compared to 64% in 2012[5,20]. This increase did not include nontraditional prostatectomy procedures, which are gaining in interest. Robotically-assisted radical prostatectomy (RALP) is currently the predominant approach for prostate cancer surgery [21] and lends itself to being managed on a short stay pathway. Musser et al.[22] illustrated an ambulatory extended recovery program for minimally invasive prostatectomy that can successfully transition most patients to a 1-night hospital stay without resulting in an increased rate of readmission.

These nontraditional outpatient oncology procedures along with the standard outpatient diagnostic biopsies have greatly increased the need of ambulatory anesthesiologists to better understand onco-anesthesia and identify optimum anesthesia clinical pathways and protocols.

Clinical Pathways and Enhanced Recovery Protocols for Ambulatory Surgery

Enhanced recovery after surgery (ERAS) is a surgical program aimed to increase quality of patient care and patient satisfaction through integrating evidence-based protocols to help standardize care, decrease health care expenditures, hospital length of stay (LOS) and surgical morbidity[23,24]. As will be discussed below, these ERAS pathways have piqued interest in the impact of anesthesia choice on cancer recurrence. The overall purpose of the ERAS pathways is to accelerate recovery by decreasing the body's response to surgical stress (physical, physiological, and psychological). The physiological chain reaction brought on by direct surgical injury results in locally released inflammatory mediators or systemic effect of cytokines, inflammatory mediators, hormones that contribute to the "stress response to surgery[25]." If left untreated the patient is catabolic, immobile, weak and, has gut dysfunction which compounds the injury, delays healing, and may lead to complications[26-28].

To achieve these goals, the surgeons strive for reducing the primary surgical injury and reducing blood loss by using minimally invasive techniques. The anesthesiologists control patient's physiology during surgery by optimizing analgesia and individualizing fluid therapy. Proper fluid therapy helps to maintain cellular perfusion, reduce extracellular fluid flux and avoid salt and water overload which leads to gut ileus. Early gut function and enteral feedings help reduce insulin resistance and restore homeostasis. Postoperatively the goal is to have early mobilization which reduce complications, i.e., atelectasis, chest infection, DVT and stimulate muscle function to maintain strength[29].

The important components of ERAS preoperatively, includes preadmission patient counseling and education, fluid and carbohydrate loading, no prolonged fasting, no/selective bowel prep, antibiotic prophylaxis, and thromboprophylaxis. Intraoperatively ERAS components include short-acting anesthetic agents, appropriate regional anesthesia/analgesia, and maintenance of normothermia (body warmer/warm intravenous fluids). The common components postoperatively include appropriate regional anesthesia/analgesia, non-opioid oral analgesia/NSAIDs, no nasogastric tubes, prevention of postoperative nausea and vomiting (PONV), and early oral nutrition and mobilization[23,26].

Most of the ERAS programs in the literature relate to colorectal surgery. Results suggest that the implementation of the ERAS programs for colorectal surgery leads to a reduction in length of hospital stay by more than 1 day and an almost 12% reduction in total complication rates in patients undergoing major surgery[30]. Studies of ERAS programs in gynecologic surgery have shown that these programs significantly reduce length of hospital stay and have positive economic benefits without increasing readmission and complication rates[31,32]. ERAS pathways are being embraced in a variety of different surgical procedures and applied more frequently in this new era of value-based care: Thoracic[33], head and neck[34-36], breast reconstruction [37-39], gastrointestinal[40,41], bariatric[42], urology[43,44] and orthopedics[45]. Overall, results illustrate that ERAS programs are associated with shorter LOS, a reduction in overall health care costs, and improvements in patient satisfaction.

A multidisciplinary team needs to be identified to plan and develop each individual ERAS program. This multidisciplinary team involves many key players including patients, anesthesiologists, surgeons, administrators, nurses, physiotherapists, dieticians, and research personnel. There are several obstacles that also need to be addressed. Implementing an ERAS program can be difficult because it mandates multidisciplinary collaboration, requires high rates of protocol compliance, requires a lot of staff education, significant financial support, variability in components of different protocols based on the different surgical procedures and lack of consistency in staffing. It is also very important, to include an audit of compliance and outcomes.

How is ERAS relevant to the ambulatory setting?
Ambulatory surgery specific ERAS pathways are limited in the literature. Many of the same main principles of ERAS pathways for inpatients are relevant to patients undergoing ambulatory and short stay surgery. As ambulatory surgery facilities expand their scope of procedures to involve more complex procedures, creating an ERAS pathway can make a difference in the success of the expansion.

The most common reasons for prolonged stay after ambulatory surgery are pain and/or post-operative nausea and vomiting (PONV) [46,47]. Overall postop pain management has not changed much in the past 2 decades. The incidence of chronic postsurgical pain varies by surgery and was reported to be as high as 20-50% following mastectomies; 20-30% in other breast surgery and 5-35% after herniorrhaphy. Several risk factors have been identified, with the one that is amenable to clinical control is the degree of postoperative pain the patient endures[48]**.** The goal of pain management should be to minimize pain through patient education and procedure specific evidence-based analgesic techniques incorporated into the ERAS pathway[49,50]. The use of opioids in postoperative analgesia results in adverse effects, such as sedation, PONV, urinary retention, ileus, and respiratory depression, which are all events that can delay discharge. Multimodal analgesia is used to achieve effective pain control while reducing opioid-related side effects is one of the most relied on principle for enhanced recovery. Successful ERAS pain management must consider perioperative combinations of non-opioid methods, including acetaminophen[51], NSAIDs[52], intraoperative dexmedetomidine[53], lidocaine, COX-2 inhibitors, NMDA receptor antagonists, glucocorticoids, beta-blockers, alpha2 agonists, capsaicin[47,48,50], and gabapentin or pregabalin[54,55]. In addition to moving towards non-opioid analgesics, regional anesthesia techniques, such as epidural blocks, transversus abdominis plane (TAP) block[56,57] paravertebral blocks[58,59] and other specific regional nerve blocks[60] are increasingly incorporated into ERAS pathways[61].

The general incidence of postoperative nausea and vomiting is approximately 50% and 30%, respectively[62]. Prophylactic multimodal antiemetic therapy should be considered on all ambulatory surgical patients. The Apfel risk score is an excellent tool for identifying patients at risk for PONV. A combination of dexamethasone 4-8 mg, IV (after induction of anesthesia) and ondansetron 4 mg, IV (at the end of surgical procedure) should be used for most patients. Patients with high Apfel scores may do well with an additional antiemetic therapy such as preoperative transdermal scopolamine or oral aprepitant[62,63]. Despite best attempts, however, patients may still experience PONV. More research is needed on genetic factors that might influence risk reduction[64].

Perioperative fluid management as a component of ambulatory ERAS starts preoperatively by encouraging the patients to drink clear liquids up to 2 hours before surgery, remain hydrated, and avoid routine mechanical bowel preparation[65,66]. Intraoperatively, the goal is to achieve a ‘zero’ fluid balance. Goal directed fluid therapy is recommended for more complex cases. Postoperatively, ERAS fluid management is meant to encourage patients to eat and drink without IV fluid infusions. IV fluid can maintain and/or restore altered physiologic parameters to normal[26,65].

We describe our experience from Josie Robertson Surgery Center (JRSC), a free-standing ambulatory surgery center at Memorial Sloan Kettering Cancer Center, where the development of ERAS pathways for ambulatory surgery was a critical component for the success of the surgery center. Development of ERAS pathways for ambulatory surgery involved extensive literature review, and multidisciplinary collaborative efforts and creation of ERAS surgery specific pathways. Creating a standardized clinical care pathway enables the anesthesia team to systematically approach the patient's care, minimizing variability and maximizing predictable outcomes. Specifically, four surgical procedures that were identified as non-traditional ambulatory surgery-short stay procedures for cancer surgery: Mastectomy with and without reconstruction; robotic prostatectomy, robotic and laparoscopic hysterectomy; and thyroidectomy.

Common elements of our ERAS ambulatory programs include: All patients receive a standardized anti-emetic protocol, which included administration of dexamethasone, ondansetron and aprepitant to patients who were high risk; Minimize opioid administration and supplement with preoperative gabapentin, IV acetaminophen and ketorolac if appropriate; minimize use of nasogastric tubes; appropriate fluid administration and standardized interventions related to the specific surgical procedure. Ambulatory surgical ERAS programs should measure their outcomes, including length of stay, pain management, need for transfer/admission to acute care hospital, return visits to ED/UCC or readmission with 30 days[67]. Measuring compliance with ERAS program is an essential assessment of clinical care pathway improvement. Bakker et al. illustrated that as adherence to ERAS elements decline over time, postoperative LOS increases. However, recommitment through auditing compliance of elements can return to improved outcome in postoperative LOS[68].

Overall implementation of ERAS pathways for ambulatory surgery provides improved outcomes with shortened postoperative length of stay, but it is only sustainable through close cooperative interdisciplinary efforts, continuous education and evaluation. Outcome data from JRSC will be presented.

Does choice of anesthesia affect patients' immediate and long term outcomes?

The actively developing field of onco-anesthesiology is specifically geared toward addressing these questions. The perioperative period is a critical point in the biology of many cancers. Several theories have been offered to help elucidate what the impact of an anesthesia intervention could have on clinical outcomes. There is a complex interplay between inflammation, immunosuppression, angiogenesis, hypothermia, and an increased catecholamine release that could facilitate the growth of minimal residual disease and promote the seeding of circulating tumor cells[69]. The preclinical and retrospective clinical trials suggest that interventions could modulate those factors and could have a major impact on cancer progression and formation of metastasis. However, it is unclear whether the same anesthetics, analgesic or techniques would have the same effect on all cancers. Most recently, Szekandarzad et al.,[70] and Kim[71] extensively reviewed the existing evidence of volatile anesthetics, NSAIDS, propofol, non-selective beta blockers for different oncological procedures. There is lack of convincing clinical evidence at this time to select one particular option or anesthesia technique to reduce cancer recurrence of improve cancer- related outcomes[70-72].

The patient's principal line of defense against cancer cell invasion and metastasis is thought to be the host's own immune response. Perioperatively, patients develop a stress response that modifies the actions of their immune system. The immune pathogenesis includes an "elimination phase" where a cancer-free state is achieved with various factors. Among the identified factors are Natural Killer (NK) cells, CD4+Th1, CD8+CTL, cytokines and tumor necrosis factor-α. Specifically, Natural Kill (NK) cell function needed for the clearance of tumor cells is impaired[70,71,73]. This inhibition could affect the process of limiting minimal residual disease and circulating tumor cells and thereby increase risk of metastasis and tumor recurrence. The immune pathway describes an equilibrium state where host's immune response keeps cancers cells in a state of dormancy and then the final "escape phase" where the tumor cells escape the host's immunity control. It is thought that anesthesia can attenuate stress response and modify immune activity primarily at the elimination phase, but perhaps residual effects throughout, thereby opening the door for many theoretical proposals of preferred anesthesia choices and their impact on these phases[74,75]. Theoretical benefits of regional anesthesia on tumor inhibition were first described in the early 1970's, but it was the retrospective study of Exadakytlos et al., in 2006[76] that suggested an association between the use of regional anesthesia and propofol and a decrease of breast cancer recurrence. Local anesthesia agents have an anti-inflammatory, opioid and volatile sparing effect and the analgesic effects of regional anesthesia provide a

theoretical basis for its positive effect on patient outcome[77]. However, to date in active clinical practice the benefits have not been definitely shown[78]. Results from active NCT clinical trials comparing regional anesthesia/analgesia techniques with GA and systemic opioids in breast center are ongoing[79]. Opioids are a maintain stay of the perioperative period, however, there is ongoing controversy as to the immune modulatory effects of various opioids. Fentanyl and morphine appear to be more immunosuppressive compared to oxycodone, hydromorphone, buprenorphine or tramadol[80]. However, human clinical data on this controversy could provide no evidence that opioids increased the risk and number of metastasis. The largest study thus far is a population-based cohort study that included 30,000 patients, and no association of opioids and breast cancer recurrence[81]. A recent systematic review and meta-analysis pertaining to animals only, concluded that NSAIDs are the class of medications with the highest efficacy in reducing the incidence and number of tumor metastases in experimental animal models[82]. However, the clinical data is very limited[83,84] and insufficient to recommend or refute perioperative NSAIDs for colon or other ambulatory cancer procedures. Propofol may have antitumor effects in animal studies and limited clinical studies measuring serum concentrations of markers for angiogenesis and metastasis suggest possible protective effect. An ongoing prospective RCT measured NK cell cytotoxicity *in vitro* in blood samples from breast cancer surgery patients preop and 24 hr. postop and found greater cytotoxicity in patients receiving PVB vs. sevoflurane/opioids[85]. Similar findings were reported by Deegan et al[86]. Whether this is attributable to propofol, local anesthesia, improved pain control, opioid and volatile sparing remains to be seen. However, there is some enthusiasm at this point to advocate for propofol/ TIVA supplemented with regional anesthesia as an attractive alternative to volatile/opioid anesthesia. Nevertheless, it would be too premature to suggest volatile anesthetics as contraindicated in cancer surgery, especially in ambulatory surgery where sevoflurane is widely used[87,88]. High levels of stress and anxiety in this population, which is translated to a physiological stress response with levels of cortisol and catecholamines, can modulate cellular immunity[89]. Animal studies using beta blockers is weak. A clinical trial is in progress evaluating the combination of COX2 and beta blockers preoperatively to reduce circulating catecholamines and prostaglandins[90] Other strategies under investigation include immune-enhancing nutrition and perioperative immune stimulation[70,91].

Current Limitations: The explanations for the ambiguity and lack of conclusive evidence stems from the majority of published clinical studies being retrospective or unplanned analysis of controlled trials, and therefore subject to bias. They weren't specifically designed to test the impact of one drug over another. Additionally, the lack of standardized definitions of survival outcome adds to the inability to interpret the results. How was recurrent or progression described? Some studies included different cancer stages and histology and lack of genomic data. Ongoing and future research need to be large enough to enroll patients with similar tumor related variables, exposure to neoadjuvant or adjuvant therapy and similar demographics, to minimize multiple confounding variables, so that the impact of anesthesia or analgesia technique can be more clearly analyzed. At this point, our focus should be on providing perioperative onco-anesthesia care that should focus on maintaining homeostasis, implementing ERAS pathways where appropriate, utilizing multimodal analgesia, prophylactic antiemetics and a stable perioperative course.

Ambulatory surgery must join the global mission of cancer surgery to "deliver safe, affordable and timely cancer care[92]." With the developing field of onco-anesthesia, anesthesiologists practicing in ambulatory surgery facilities can contribute significantly to patient outcomes by expanding their surgical procedures, implementing ERAS protocols, and selecting an evidenced based anesthesia technique for improving cancer outcomes.

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Nerve Injury after Peripheral Nerve Block: Evaluation, Management, Best Practices, and Medicolegal Concerns

H. David Hardman, MD, MBA **Chapel Hill, North Carolina**

Introduction

Nerve injury after peripheral nerve blockade (PNB) for surgical procedures and post-operative pain relief continues to be a source of attention and concern for patients, anesthesiologists, and surgeons, despite significant advances in training and equipment technology for nerve localization. When a significant nerve injury is recognized for the first time after surgery, a cascade of events can be set into motion leading to strained professional relationships between anesthesiologists and surgeons, not to mention the potential for medicolegal action by patients.

Incidence of nerve injury after peripheral nerve block and risk factors

The absence of a standard definition of nerve injury after surgery has hampered understanding of the incidence and severity of the problem. The use of the term, post-operative neurologic symptoms (PONS), or peripheral nerve injury (PNI), is an attempt to adopt a standard definition of incidence, without describing severity or causation. Temporary sensory and motor injuries are common; permanent motor injuries are rare. In contrast to neuraxial blocks, up to 19% of patients receiving PNBs may report sensory or motor abnormalities on the first post-operative day after surgery, decreasing to 2% three months later, with less than 0.2% persisting beyond 1 year.[1-3] Among elective procedures, orthopedic arthroscopic and open shoulder procedures report some of the highest overall injury rates, with diffuse brachial plexus injuries, as well as single nerve injuries to the axillary, musculocutaneous, suprascapular and radial nerves.[3] Fortunately, long term severe injuries (motor loss or significant neuropathic pain) lasting longer than 6-12 months are exceeding rare, with level III evidence consistently demonstrating an incidence of 2-4 severe nerve injuries per 10,000 PNBs, in both the pre (nerve stimulation) and post-ultrasound introduction era.[4-9]

In clinical practice, it is not unusual for surgeons to assume that a regional anesthesia technique is the cause of a newly discovered post-operative neurologic injury. This attitude reflects a lack of understanding of the current literature. The differential diagnosis should always consider patient related, surgery related, and anesthesia related causes. Although causation may be difficult to determine at times, there are many high quality studies that can shed light on this controversy. Three large single-institution clinical registries reporting the incidence of nerve injury after elective orthopedic joint replacements for hip, knee and shoulder surgery, have demonstrated that PNB does not increase the risk of PONS; on the contrary, in patients having shoulder replacement the odds of a PNI was reduced by about 50%.[10] Further evidence that PNB is not associated with increased risk of PONS comes from a large case series of over 7,000 PNBs associated with a variety of surgical procedures, with a neurologist determining causation of long term severe injuries, based on the results of electrodiagnostic studies. The authors of this study concluded that non-anesthesia related causes of injury were 9 times more likely than anesthesia related causes.[7] Lastly, a large single institution case series of over 380,000 surgical procedures during a 10 year time interval, was not able to identify PNB as an independent risk factor for the development of PONS. On the other hand, patient related risk factors such as diabetes mellitus, hypertension, and tobacco use, as well as surgery procedure types (neurosurgery, cardiac surgery, orthopedic surgery, and general surgery), were all demonstrated to be independent risk factors for the development of PONS.[6]

What can we conclude from this information? A postoperative neurologic injury is most likely multifactorial in nature, and although an anesthesia related cause should be part of the differential diagnosis, it should never comprise the entire differential diagnosis, as other causes are more common, including surgery specific procedures. Patients with underlying microvascular disease (tobacco use, hypertension, diabetes) and those with chemotherapy-induced neuropathy (CIPN) (cisplatin, oxaliplatin, carboplatin, vincristine, paclitaxel, suramin), especially those with sub-clinical injury, are at risk for post-operative double crush injuries, which may manifest as new clinical nerve deficits post-operatively.[6,11]

A recent publication from the 2nd ASRA Practice Advisory on Prevention of Neurologic Complications after regional anesthesia cites class II recommendations to conclude that PNB may increase the risk of new or progressive deficits in patient with diabetic peripheral neuropathy (DPN), and also recommends decreasing the concentration of local anesthetic, total volume, and eliminating or reducing the concentration of adjuvant vasoconstrictors (epinephrine).[1,11] Patients with central nervous system disorders such as multiple sclerosis, amyotrophic lateral sclerosis, and post-polio syndrome may have subclinical injury, along with a natural waxing and waning of the disease, which may be exacerbated after surgery. Although there is insufficient evidence to suggest that PNBs may increase the risk of PONS in these patients, if it occurs, it may be incorrectly attributed to the PNB. The decision to offer a PNB in these patients should be individualized after a risk-benefit discussion.[11] Consideration may also be given to performing blocks after surgery, in patients at higher risk for developing complications, after a postoperative neurologic assessment has been completed.

Mechanisms of nerve injury and classification system

Each individual axon is surrounded by a connective tissue layer known as the endoneurium. Individual axons are packed together to form fascicles (100-1000 µm diameter), surrounded by a circumferential impermeable connective tissue layer (perineurium), containing non-fenestrated capillaries. Collections of fascicles are then further surrounded by an outermost connective tissue layer, (epineurium), which is a thick, but permeable layer. Deep to the epineurium, but between fascicles (interfascicular) lies a loose areolar connective tissue layer, composed of adipose cells, fibroblasts, mast cells, arteries, arterioles, veins, capillaries, and lymphatics. This layer is also known as the sub-epineurium.

Although nerves are delicate structures, their connective tissue architecture affords several layers of protection to prevent direct axonal injury. A variety of mechanisms can injure the axonal and connective tissue components of the nerve, resulting in demyelination and or axonal loss, with disruption of electrical conduction. These injuries can include stretch and compressive forces; ischemia; blunt and penetrating trauma; thermal injury; tissue edema; hematoma formation; toxic or metabolic injuries; and inflammatory or infectious etiologies.[12] Mechanisms of injury can be surgery related (positioning, tourniquets, retractors, scalpel, hematoma, edema, thermal, inflammatory), patient related (ischemic, inflammatory), or anesthesia block related (needle trauma, inflammation, hematoma, local anesthetic toxicity).[12,13] Although nerves tend to pinwheel away from a compressive force exerted by an advancing block needle in clinical settings, if a block needle penetrates the epineurium, inflammatory changes will occur.[14] However, the major danger appears to be associated with intrafascicular penetration, and subsequent generation of high intrafascicular pressures causing ischemia, either with or without fascicular disruption. These changes can occur experimentally even with injections of saline, although local anesthetic injections are much more neurotoxic.[12, 13] Advancing short bevel block needles of sizes and diameters commonly used clinically, directly into fascicles, is difficult to achieve experimentally, due to the resistance encountered trying to penetrate the tough perineurium, as well as due to the large diameter of needles relative to fascicle size. Nerve fascicles range in size from 100-1000 µm, while a 22 gauge block needle is 700 µm in diameter.[13] Unfortunately, block needles can also injure the nerve fascicles by disrupting small vascular structures in the interfascicular space (sub-epineurium), creating intraneural hematomas, which can subsequently compress nerve fascicles. Additionally, block needles coming in close proximity to the nerve may disrupt the external vasa nervorum, leading to hematoma formation outside the epineurium, which may cause nerve compression and ischemia.

Nerve injury can be graded based on anatomic levels of injury, which also provide a clinical prognosis.[12,15,16] The Seddon classification divides injury into three grades; neurapraxia (myelin injury only), axonotmesis (axon injury only), neurotmesis (axon injury and connective tissue disruption involving the endoneurium, perineurium, and epineurium). Neurapraxic injuries will resolve spontaneously with full recovery, axonotmetic injuries have a mixed prognosis for spontaneous recovery and may require surgical intervention, while neurotmetic injuries require surgical nerve reconstruction with mixed outcomes. Motor nerve injury on clinical exam is graded on the following 6 point British Medical Research Council (MRC) scale: 0=no visible twitch; 1=visible twitch; 2=movement insufficient to overcome gravity; 3= movement sufficient to overcome gravity; 4= movement against gravity plus additional resistance; 5=normal strength.[16]

The Sunderland classification system further refines the Seddon system, to clarify the level of connective tissue disruption. Sunderland grade 1 and grade 2 correspond to neurapraxia and axonotmesis, grade 3 is considered

neurotmesis with disruption of endoneurium continuity, grade 4 is neurotmesis with disruption of endoneurium and perineurium continuity, while grade 5 is complete nerve transection, including disruption of the epineurium. In general, nerve reconstruction surgery tends to have a poorer prognosis with Sunderland grade 4 or higher injury level.[16] The overwhelming majority of patients diagnosed with PONS see complete resolution of their symptoms within 3 months; hence, most injuries are neurapraxic, or Sunderland grade 1 injuries.

The clinical challenge is to diagnose Sunderland grade 3 or higher injuries as soon as possible, in order to provide counseling and surgical referral on a timely basis. In general, nerve reconstructive functional outcomes are improved with earlier surgery, usually between 6 and 9 months, although recovery has been reported with repairs initiated up to 18 months after injury.[16] On the other hand, when spontaneous recovery occurs, outcomes are usually better than with reconstructive surgery, with the full extent of possible recovery not being apparent for up to two years.[16] This may create tension between the anesthesiologist advocating watchful waiting, hoping for complete neurologic recovery, and the surgeon pressing to go ahead in order to obtain the best reconstructive result with nerve grafting or nerve transfers.

Evaluation of neurologic symptoms after surgery: Imaging (US, MRI, MRN) and electrodiagnostic testing (NCS, EMG)

Early recognition and documentation of PONS is important for several reasons, including diagnostic and therapeutic interventions for reversible lesions, such as hematoma evacuation, as well as for medicolegal protection. Barriers exist to early recognition of PONS secondary to patients' residual sedation and misunderstanding of the significance of extended duration of motor or sensory nerve loss after surgery. The presence of casts, splints, stabilization devices and dressings may impair a patient's perception of motor or sensory abnormalities and contribute to a delay in diagnosis. An urgent neurology consult is warranted in any patient with significant motor or sensory loss that persists beyond the expected duration of the block. A recent review article presents an algorithm for the evaluation and management of a new postoperative neurologic deficit following regional anesthesia.[15]

The goal of imaging or electrodiagnostic testing (EDX) is to help determine the location, severity, and prognosis for recovery of the neurologic abnormality; unfortunately, EDX cannot always establish causation (surgery, anesthesia, patient).[17] EDX is also useful in demonstrating the presence of a pre-existing neurologic lesion that may not have been clinically apparent prior to surgery. High resolution (12-20 MHz) ultrasound (US) is being increasing utilized as part of the initial evaluation of PONS, in order to help localize and define the severity of the lesion.[18] US images of affected peripheral nerves can be traced along the course of the nerve and spot potential disruption in nerve continuity, consistent with neurotmetic injury, which can be verified with magnetic resonance imaging (MRI) or magnetic resonance neurography (MRN). However, the lateral and axial resolution of US is superior to that of MRI/MRN. Non-specific pathology visualized with US imaging includes increases in cross-sectional nerve area (CSA), along with loss of fascicular detail, as compared to the asymptomatic side.[18] MRN is a term used to signify alterations in processing of the conventional MRI signal in order to enhance peripheral nerve imaging. A two-dimensional T1 fat suppressed and T2 enhanced water weighted signal will display the outline of nerve roots, plexus and peripheral nerves, and display a bright or hyperintense image in areas with increased water content associated with edema. Unfortunately, this signal is not able to distinguish between neural edema associated with less severe injuries, such as neurapraxia, versus more serious axonotmetic or neurotmetic injuries. [16] MRI imaging is also able to demonstrate early denervation injuries (axonal) in muscle, before they become apparent on EMG examination.[16]

The utility of EDX studies lies in their ability to localize the site of injury in the peripheral nervous system (nerve roots, plexus, proximal peripheral nerve, distal peripheral nerve) and to distinguish between demyelination and axonal injury, and hence prognosis for recovery.[19] EDX studies consist of nerve conduction studies (sensory and motor), along with needle electromyography. Compound motor nerve potentials (CMAPs) are measured bilaterally by stimulating peripheral nerves suppling normal and abnormal muscles. Nerves are stimulated proximally and distally, with muscle depolarization associated with individual fibers summated together and measured with surface electrodes on target muscles. A characteristic signal is obtained with measurement of latency, amplitude and duration. Latency measures onset of depolarization of the fastest myelinated fibers, while amplitude reflects the summation of individual muscle fiber depolarization potentials based on the number of axons recruited with supramaximal stimulation current.[19] Duration is a reflection of synchrony and efficient muscle contraction. Signals are biphasic or triphasic in nature, with deflections above baseline described as negative by convention, and those

deflections below baseline being described as positive.[19] Sensory nerve action potentials (SNAPs), as well as CMAPs are commonly measured. SNAPs are low amplitude (μA), short duration (1-2mS) signals, as compared to CMAP higher amplitude (mA), longer duration (5-6mS) signals. Temporal dispersion and phase cancellation have a greater effect on SNAPs versus CMAPs, and in cases of severe neuropathic injury, SNAPs may be difficult or impossible to detect.[19]

In general, demyelination injuries are characterized by slower conduction and increased latency (conduction velocity <75% of lower limit of normal, latency > 130% of normal).[19] As conduction velocity slows, temporal dispersion and wave phase cancellation will occur, with increasing time separation of depolarization signals from faster and slower fibers, leading to an increase in duration, and a decrease in measured peak amplitude of CMAP and SNAP signals. When demyelination is focal and severe enough to prevent depolarization, the term "conduction block" is used to describe this phenomenon. The site of injury can be determined by progressively stimulating the peripheral nerve of interest from distal to proximal, until a jump in latency is detected, or in the case of conduction block, no CMAP is detected.

Axonal injuries are characterized primarily by a decrease in peak amplitude, with limited effect on conduction time and latency. Conduction velocity is within 75% of the lower limit of normal conduction velocity, while latency is within 130% of the upper limit of normal.[19] Unlike demyelinating injury, once axonal injury occurs, within 3-5 days, Wallerian degeneration prevents depolarization distal to the site of injury, and CMAPs and SNAPs can no longer be detected at distal muscle or sensory sites innervated by the affected nerve. However, within the first several days after injury, the nerve is still electrophysiologically active distal to the site of injury, and can still be stimulated, generating distal CMAP and SNAP potentials. This phenomenon is known as a pseudo-conduction block since it mimics a demyelination conduction block.[17, 19]

EMG studies confirm the results obtained by nerve conduction studies, and provide additional localization information for proximal injury sites than cannot easily be measured with NCS. Denervation potentials measured with needle EMG (fibrillation waves, positive sharp waves) are never associated with demyelination injuries; when present they indicate more serious axonotmetic or neurotmetic injuries.[17,19] The presence of denervation potentials imply injury to the nerve at or proximal to the branch point of the most proximal muscles with denervation potentials. [19] EMG studies also assess the number and type of motor unit action potentials (MUAP), and measure recruitment and activation of motor units. MUAPs can sometimes be detected, when asking a patient to try and contract a muscle, even when no visible motor activity is apparent on clinical exam. This is a positive sign, and indicates that partial innervation is still present, without neurotmetic injury. However, this pattern cannot distinguish between severe demyelinating injury versus axonal injury, as in either case, recruitment of additional motor units will be impaired.[19] After several weeks, the underlying etiology will become apparent, as a demyelinating injury will rapidly recover and motor unit recruitment will increase or return to normal. Abnormal recruitment of motor units appears as a "picket-fence" tracing pattern on EMG exam; normal recruitment appears as a "complete interference" pattern on EMG exam, with no space between adjacent MUAP spikes.[19]

The change in morphology of MUAPs is used to follow the presence of reinnervation after axonal injury. With moderate injury, normal motor units adjacent to injured motor units will send out collateral branch point sprouts to innervate adjacent muscle fibers innervated by damaged nerves. This will increase the size of the motor unit (number of fibers innervated by a given axon), and increase the duration and number of phases of the MUAP. These collateral sprouts are initially unmyelinated, and appear as delayed low amplitude satellite potentials.[19] With increasing severity of injury, no normal adjacent motor units exist, and collateral branching cannot occur. Axons can only extend unmyelinated growth sprouts from the proximal uninjured axon stump. These low amplitude potentials connote more severe injury and are termed nascent potentials.[19]

EDX studies are typically obtained initially 3-4 weeks after injury, when the most information is obtainable from a single study.[15] The exam can be uncomfortable, since small caliber 25 gauge unipolar recording needles are inserted multiple times in a variety of different muscles, in a non-sedated patient. Pathologic denervation potentials associated with axonal injury are first detected in muscle 3-4 weeks after injury, when CMAP and SNAP amplitude loss due to Wallerian degeneration will be complete in NCS.[15,17,19] Demyelinating injuries can be reliably distinguished from axonal injuries at this time, and patients can be either reassured about the prospects of full

recovery, or counseled about the possibility of partial recovery and the potential need for future reconstructive surgery. With evidence of moderate to severe axonal injury, EDX studies can be repeated at 3 months and 6 months to assess the presence and magnitude of reinnervation, with referral to a reconstructive peripheral nerve surgeon for injuries not demonstrating further improvement.

An alternative approach is to obtain EDX studies several days after the initial injury is manifested, which several authors advocate.[16,17] The advantage of an early exam is the ability to demonstrate a pre-existing injury with reinnervation, characterized by polyphasic, long duration MUAPs with satellite or nascent potentials, along with the presence of positive sharp waves and fibrillation potentials. These EMG changes are consistent with chronic injury, and would not be detectable until at least 3-4 weeks after injury. Delaying initial EDX studies until one month after injury would limit the ability to establish that an injury was present prior to the surgical and anesthetic procedure, and not caused by it. Early EDX studies in the setting of axonal injury, prior to complete Wallerian degeneration, also allow the ability to localize the site of the neuropathic lesion. Normal distal muscle CMAPs will still be manifested, as the nerve stimulating site moves distal to proximal, until the stimulating needle is at the level of injury. After Wallerian degeneration, abnormal distal CMAPs will be measured at any point along the nerve, including proximal needle stimulating sites where the nerve is undamaged.

During the recovery process, a regular program of physical therapy should be prescribed in order to maintain joint range of motion and prevent flexion contractures, utilizing splints if needed.[15] Neuropathic pain can be managed with a tiered approach, utilizing first line agents such as tricyclic antidepressant secondary amines (nortriptyline, desipramine) or SSNRI's (duloxetine), gabapentinoids (gabapentin, pregabalin), and topical 5% lidocaine patches.[15] Opioids may be considered as second-line agents.

Reconstructive surgical options and pain management for severe injuries

Peripheral nerve reconstruction surgery should be considered for any persistent serious motor nerve injury on clinical exam (MRC grade 0-3) that affects shoulder, elbow or hand function, with minimal evidence of reinnervation on EDX studies at 6 months.[16] Axon regeneration occurs at a rate of about 1 mm per day, or 1 inch per month, but until distal reinnervation occurs, deterioration continues in the muscle fiber, neuromuscular junction, and endoneurial tunnel basement membrane.[16] Irreversible functional changes in target tissues will occur between 1-2 years after denervation, leaving reinnervation moot, with muscle and tendon transfers from normally innervated tissue the only option to partially restore function. When neuropathic injury is distal, there may be sufficient time for spontaneous reinnervation; however, with proximal injury, surgical reconstruction is more likely to be required. Neurotmetic injuries with complete nerve transection (Sunderland 5), should be surgically repaired as soon as possible, in order to prevent painful neuroma formation.[16] A sharp, clean transection (unlikely with a block needle) should be repaired immediately before stump retraction occurs. There are multiple options to repair nerves and restore function. In general, best results are obtained when the proximal and distal nerve stumps can be trimmed and directly opposed with microsurgical techniques involving fascicular reattachment and restoring epineural continuity. However, if the resulting neurorrhaphy has any residual tension, the repair is likely to scar with neuroma formation, leading to a poor functional outcome. In this setting, an autologous nerve interposition graft, harvesting a non-critical nerve such as an intercostal, sural, superficial radial, or lateral antebrachial cutaneous nerve, is used to bridge the gap. For best results harvested sensory nerves are used to repair sensory nerve injuries, while mixed or motor nerves are used to repair motor nerve injuries.[16]

Since the late 1990's, treatment has shifted from interposition grafts to nerve transfer techniques, where improved results have been obtained (MRC 3-4), especially in the setting of proximal injuries, by mobilizing the distal portion of a viable nerve branch, and connecting it to the distal portion of the denervated nerve, close to the target muscle.[16] For example, in the setting of an injury to the suprascapular nerve and axillary nerve, shoulder abduction can be restored by mobilizing the distal portion of the spinal accessory nerve, thereby denervating the lateral aspect of the trapezius, and connecting the mobilized segment of the spinal accessory nerve to the distal portion of the suprascapular nerve (end to end or end to side), restoring function to the supraspinatus and infraspinatus muscles. To further improve function and restore abduction, a terminal branch from the radial nerve supplying either the long or medial heads of the triceps can be mobilized, without adversely affecting triceps strength, and connected to the distal anterior branch of the axillary nerve to restore function to the deltoid and teres minor muscles. Using the same concept, in the setting of a musculocutaneous nerve injury, elbow function can be

restored by mobilizing a proximal branch of the ulnar nerve, containing fascicles innervating the flexor carpi ulnaris muscles (without compromising wrist flexion), and connecting them to a branch of the musculocutaneous nerve near the biceps muscle. Clearly, this is demanding, extensive and meticulous surgery, requiring intraoperative nerve stimulation and microsurgical suturing technique, along with an extended recovery period. Even the best outcomes will not completely restore pre-injury strength and function.

Best practices to prevent nerve injury

The 2nd ASRA Practice Advisory on Neurologic Complications Associated with Regional Anesthesia updates the previous 2008 version, and offers guidance on potential best practices to potentially reduce the risk of block related nerve injury.[1] This is not a standard of care, nor is it a guideline, due to the limited evidence basis underlying the recommendations. Adherence to the advisory is intended to provide optimal care, but cannot guarantee the avoidance of adverse outcomes. As in the previous advisory, the current advisory recommends against a routine practice of deep sedation or general anesthesia when performing regional anesthetic procedures in adults, although the practice in children does not appear to increase baseline risk. However, a recent publication challenges the Practice Advisory recommendation not to perform nerve blocks in adults under regional anesthesia, and suggests that subsets of patients may benefit from fascial plane blocks performed under general anesthesia, such as pectoralis blocks (PecI&II) and transversalis plane blocks, without incurring additional risk.[20] The Practice Advisory also affirms that there are no data to demonstrate superiority of one nerve localization technique over another (ultrasound, nerve stimulation, paresthesia technique) with respect to reducing the incidence of PNI. Other important points include the following: 1) the presence of an evoked motor response at a current of <0.5 mA indicates needle-nerve contact, or intraneural needle placement [21]; 2) there are no human data that confirm or refute the effectiveness of injection pressure monitoring for limiting PNI; 3) the practice of subjectively assessing injection pressure by hand feel is inaccurate [22] ; 4) ultrasound can detect intraneural injection [23]; 5) intraneural needle insertion does not invariably lead to functional nerve injury [24,25]; 6) intrafascicular needle insertion and injection should be avoided since it can cause histological and/or functional nerve injury; 7) ultrasound does not have the resolution to distinguish between interfascicular and intrafascicular injection; 8) adequate images of needle-nerve interface are not consistently obtained by all operators in all patients. A simple and inexpensive technique to measure and limit opening injection pressure during PNB has been described, utilizing a compressed air injection technique, by inserting an air bubble in the injection syringe, and limiting compression to < 50% of the initial bubble volume.[26]

Although not addressed in the recent advisory, all local anesthetics are neurotoxic, myotoxic, and cytotoxic in animal experimental in vitro models. However, there is no clinical evidence to choose one local anesthetic in favor of another in order to reduce the likelihood of PNI. Adjuncts such as clonidine, buprenorphine, dexamethasone, and dexmedetomidine appear to be safe in commonly used perineural concentrations, and show less neurotoxicity than ropivacaine in animal models. [27,28] Lastly, there is accumulating evidence to suggest that depositing local anesthetic at a distance farther away from the target nerves, in muscle or fascial planes, may be equally effective in producing a successful block compared to deposition of local anesthetic adjacent or circumferential to the nerve.[29] Although yet to be proven, this practice could potentially decrease the likelihood of needle-induced nerve injury.

Medicolegal concerns and risk reduction

A review of the ASA closed claims data from 1990-2007 demonstrates that only 2% of all malpractice claims were related to PNBs.[30] Most of these claims were for temporary injuries of all types, while a majority of all claims involved nerve injury. Two-thirds of the nerve injury claims were felt to be block-related by the reviewers. Unfortunately, malpractice risk occurs with PNBs, even when injuries are only temporary in nature. Given that the benefits of PNBs are short term (enhanced quality of recovery), and that catastrophic debilitating outcomes are possible, it is imperative to discuss and document the possible serious complications that can occur, including permanent nerve injury.[31] The results of a survey of academic anesthesiologists performing regional anesthesia indicates that there is room for improvement with respect to disclosure of serious complications related to regional anesthesia.[32] The option to choose regional anesthesia should always be part of a shared decision making process between the patient and the anesthesiologist, after a discussion of the material and patient specific risks, without coercion from anesthesiologists or third parties, including surgeons, and documented on an anesthesia consent form separate from the surgical consent form. Consideration may be given to offering PNB after a surgical procedure, after neurologic status has been documented, for patients deemed to be at higher risk for developing PONS.

Should a patient suffer a serious nerve injury after a PNB, and decide to hire a plaintiff's attorney to pursue litigation, in order to prove malpractice, the attorney will need to introduce evidence to convince a jury that the physician breached the standard of care, and that by breaching the standard of care, an otherwise preventable injury occurred. Given the multifactorial nature of PNI after surgery, this is a high hurdle to overcome. Frequently, these cases may hinge on a physician's ability to demonstrate that deliberate intraneural injection did not occur, either via documented nerve localization techniques or by lack of compromise of patient awareness and communication abilities during the block procedure. Fortunately, the electronic medical record can be a powerful tool to capture detailed information related to the block process, and defend your practice against negligence, should a serious PNI occur.

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Anesthesia for Non-obstetric Surgery During Pregnancy

YaakovBeilin, NY **New York, New York**

Introduction

The incidence of surgery for non-obstetric procedures during pregnancy is between 0.3%-2%.[1,2] As there are approximately 4,000,000 deliveries per year in the United States this translates to 80,000 anesthetics for non-obstetric procedures to pregnant women per year, and most likely more due to surgery performed prior to clinical recognition of the pregnancy. Studies have demonstrated that many women presenting for surgery are unaware that they are pregnant. Unknown pregnancies in women presenting for surgery occurs in roughly 0.3%-1.3%[3,4] of adults and 2.4% of adolescents between the age of 15 and 20.[5] For this reason a urinary pregnancy test should be strongly considered in women of child-bearing age prior to surgery, unless an emergency clinical situation precludes this.

Surgery may be required at any time during pregnancy, though a large Swedish study of 720,000 patients found it was most common during the first trimester (42%), followed by the second (35%) and third (24%).[2] Appendectomy is the most frequently performed non-obstetric operation during pregnancy.[6] However, almost every type of surgical procedure has been successfully performed on the pregnant patient, including open heart procedures with cardiopulmonary bypass,[7] neurosurgical procedures requiring hypotension and hypothermia,[8] and liver transplantation.[9]

Anesthesia for the pregnant woman is one of the rare situations where the anesthesiologists must be concerned about two patients, the mother and the unborn fetus. Provision of a safe anesthetic requires an understanding of the physiologic changes of pregnancy and the impact of anesthesia and surgery on the developing fetus. Maternal considerations result from the physiology of pregnancy that affects almost every organ system. Fetal concerns include the possible teratogenic effects of anesthetic agents, avoidance of intrauterine fetal asphyxia and prevention of premature labor.

Maternal Considerations - Physiologic changes of pregnancy (Table 1)

The pregnant woman undergoes significant physiologic changes to allow adaptation for the developing fetus.

Respiratory System

Due to increased progesterone levels during the first trimester, minute ventilation is increased by almost 50% and remains so for the remainder of the pregnancy. Because anatomic dead space does not change significantly during pregnancy, at term, alveolar ventilation is increased by 70%. From 20 weeks gestation, the functional residual capacity (FRC), expiratory reserve volume and residual volume begin to decrease as a result of upward displacement of the diaphragm by the gravid uterus; this reaches its maximum reduction of 20% by term Vital capacity is not appreciably changed from pre-pregnancy levels. The increase in minute ventilation leads to a decrease in $PaCO_2$ to approximately 30 mm Hg. Arterial pH remains unchanged because of a compensatory increase in renal excretion of bicarbonate ions. The increased alveolar ventilation and reduced FRC lead to a more rapid uptake and excretion of inhaled anesthetics. The decrease in FRC in conjunction with increases in cardiac output, metabolic rate, and oxygen consumption lead to a much greater risk of arterial hypoxemia during periods of apnea or airway obstruction.

Anatomic changes to the airway include laryngeal and pharyngeal edema that can make ventilation and laryngeal visualization and tracheal intubation more difficult. In addition, mucosal capillary engorgement can cause bleeding during airway manipulation. Mallampati scores have been found to increase during pregnancy - Pilkington et al.,[10] found the incidence of grade 4 airways increased by 38% from the 12th to the 38th week of pregnancy. Together with inherent weight gain and enlargement of breasts, these changes make tracheal intubation more difficult, as evidenced by failed intubation, a well-recognized cause of maternal mortality.[11]

Cardiovascular System

Cardiac output is increased by 30-40% during the first trimester and 50% at term. This is primarily due to an increase in stroke volume (30-40%), and secondarily to an increase in heart rate (15%).[12] Further rises in cardiac output occur during labor and immediately postpartum. Blood pressure normally decreases during pregnancy because of a fall in systemic vascular resistance due to the vasodilatory effects of estrogen and progesterone. Near term, 10-15% of patients have a dramatic reduction in blood pressure in the supine position, often associated with diaphoresis, nausea,

vomiting, pallor and changes in cerebration. This is known as the supine hypotensive syndrome and is caused by compression of the inferior vena cava and aorta by the gravid uterus.[13] This can begin as early as the second trimester and may lead to a reduction in renal and uteroplacental blood flow. Symptoms can be alleviated by tilting the patient on her left side.

Compression of the inferior vena cava by the gravid uterus leads to dilatation of the azygos system and the epidural veins. Epidural venous engorgement decreases the volume of the epidural and intrathecal spaces - drugs used in neuraxial blockade should therefore be decreased.

Gastrointestinal System

Traditionally, gastric emptying was considered prolonged in the pregnant woman by the end of the first trimester.[14,15] This was thought to be related to progesterone and mechanical changes as the stomach is displaced upward by the enlarging uterus. However, recent studies using acetaminophen absorption have not found a difference in gastric emptying in pregnant women. Wong et al., found no difference in gastric emptying between term women who ingested 50 mL vs. 300 mL of water in both non-obese[16] and obese women.[17] This is in contrast to active labor when gastric emptying is delayed.[18] Although gastric emptying per se may not be delayed until the onset of labor, when the gravid uterus enters the abdominal cavity at 20 weeks' gestation bariatric pressure is increased. In addition there is an increase in the acidity of gastric secretions and a reduction in lower esophageal sphincter tone due to the influence of hormones.[19]

Hematologic system

Intravascular volume is increased by 45% during pregnancy due to an increase in plasma volume. Since this increases by a greater proportion than the red blood cell volume (55% and 30% respectively) there is a relative anemia during pregnancy. Nevertheless a hemoglobin concentration of less than 11 g/dL is considered abnormal. Most of the coagulation factors are elevated during pregnancy and consequently pregnancy is considered a hypercoagulable state, with an increased risk of thromboembolic events.[20] Platelet counts generally decrease by approximately 20% during a normal pregnancy; approximately 7% of all parturients will present with a platelet count < 150,000·mm-3, and 0.5-1% will present with a platelet count < 100,000·mm^{-3}.[21]

Hepatic Changes

Laboratory tests of liver function are commonly abnormal during pregnancy, though this does not necessarily indicate abnormal liver function. Pseudocholinesterase activity declines by as much as 20% during the first trimester and remains at this level for the remainder of the pregnancy.[22] However, prolonged apnea is rarely a problem following a standard dose of succinylcholine and the duration of ester-linked local anesthetics are not prolonged.

Nervous System

The minimum alveolar concentration (MAC) for inhaled anesthetics is decreased by up to 40% during pregnancy due to progesterone and endorphins and begins in the 1st trimester. Additionally, progesterone may increase the sensitivity of nerves to local anesthetics since neuraxial drug requirements decrease prior to uterine enlargement.[23]

Fetal Considerations

Drug teratogenicity

A teratogen is a substance that produces an increase in the incidence of a particular defect during fetal development that cannot be attributed to chance. In order to produce a defect, the teratogen must be administered in a sufficient dose at a critical point in development. In humans this critical point is during organogenesis, which extends from 15 days to approximately 60 days gestational age. However, the central nervous system does not fully develop until after birth, hence the critical time for the central nervous system may extend beyond gestation.

Well controlled randomized human studies are essentially impossible to perform due to ethical limitations and the large number of patients required to study these rare defects.[24] Four approaches have been utilized to study the effects of anesthesia in the pregnant patient: 1) animal studies, 2) retrospective human studies, 3) studies of chronic exposure of operating room personnel to trace concentrations of inhaled anesthetics, and 4) outcome studies of women who underwent surgery while pregnant.

Animal Studies

Almost all anesthetic agents have been found to be teratogenic in some animal model. However, the results of animal studies are of limited value because of species variation and the doses of anesthetic agents in animal studies were generally in greater concentrations than those used clinically. In addition other known teratogenic factors such as hypercarbia, hypothermia and hypoxemia were either not measured or not controlled. Species variation is particularly important. Thalidomide has no known teratogenic effects on rats and was approved by the United States FDA for use in humans. However it later became apparent that thalidomide is teratogenic in humans.[25]

The United States FDA has established a risk classification system to assist physicians as they weigh the risks and benefits when choosing therapeutic agents for the pregnant woman (Table 2).[26] To date there are only five drugs known to be teratogens and none of them are anesthetic agents; Category X: thalidomide, isotrentinoin, coumarin (Warfarin), valproic acid, and folate antagonists,.[27] Most anesthetic agents have been assigned a Category B or C classification (Table 3). Only the benzodiazepines have been assigned as category D (Positive evidence of risk. Investigational or post-marketing data show risk to the fetus.) Nevertheless, potential benefits may outweigh the potential risk.

Nitrous Oxide

Nitrous oxide is a known teratogen in mammals and rapidly crosses the human placenta.[28,29] It had been presumed that the teratogenicity of nitrous oxide in animals is related to its oxidation of vitamin B_{12}, which then cannot function as a cofactor for the enzyme methionine synthetase - essential for the formation of thymidine, a subunit of DNA. There is some evidence that the effects in animals of nitrous oxide are not related to these proposed effects on DNA synthesis. Pretreatment of rats exposed to nitrous oxide with folinic acid, which bypasses the methionine synthetase step in DNA synthesis, does not prevent congenital abnormalities,[30] or suppression of methionine synthetase occurs at low concentrations of nitrous oxide[31] - concentrations found safe in animal studies.[32] Despite these theoretical concerns, nitrous oxide has not been found to be associated with congenital abnormalities in humans.[1, 2, 33, 34]

Benzodiazepines

The use of sedatives, in particular benzodiazepines, in the first trimester of pregnancy is controversial. Benzodiazepines exert their action through the inhibition of gamma-aminobutyric acid (GABA) receptors in the central nervous system. GABA inhibition has been shown to inhibit palate shelf reorientation leading to cleft palate formation.[35] Some investigators in human retrospective studies noted an association between diazepam ingestion in the first six weeks of pregnancy and cleft palate.[36,37] These findings have been questioned by the results of two prospective studies that did not demonstrate an association.[38,39] It is important to note that in the studies that found an association, the assessment was in women chronically exposed to benzodiazepines and not in women with a one-time low dose exposure as typically occurs during surgery. The FDA has assigned benzodiazepines a Class D designation and although controversial,[40] this author prefers not to use benzodiazepines during nonobstetric surgery unless there is a compelling reason to do so.

Human studies:

There have been two approaches to assess the effects of anesthetic agents on pregnancy outcome: large retrospective epidemiologic surveys of women chronically exposed to anesthetic gases, and retrospective database studies comparing women who underwent surgery while pregnant to those who were not.

Epidemiologic studies

A number of epidemiologic studies were performed in the 1970's to determine the health hazards of chronic exposure to anesthetic gases including birth defects and spontaneous abortions.[4142] All the studies found similar results and the most consistent finding was that the rate of miscarriage among exposed women is approximately 25-30% greater than non-exposed women. However, all these studies were later criticized for their lack of a control group, low response rate to questionnaires, recall bias, and statistical inaccuracies.[43,44]

Outcome studies of women who had surgery while pregnant

There have also been a number of retrospective studies of pregnant women who had undergone surgery to seek an association between anesthesia and surgery and congenital defects, spontaneous abortions or fetal demise. The largest study to date was performed by Mazze and Kallen.[2] They linked the data from three Swedish health registries - the Medical Birth Registry, the Registry of Congenital malformations, and the Hospital Discharge registry for the 9 year

period 1973-1981. They examined the data for four adverse outcomes; congenital defects, stillborn infants, infants born alive but who died within 7 days, and infants with a birth weight < 1,500 grams and < 2,500 grams. They found 5,405 women had undergone surgery during their pregnancy from a total of 720,000 pregnancies. In their data set, most procedures were performed during the first trimester (41.6%), and the incidence decreased during the second (34.8%) and third (23.5%) trimesters. Most of the cases (54%) were done with general anesthesia, almost all of them (>98%) with nitrous oxide. They were not able to find an increase in congenital abnormalities or stillborn births among those who underwent surgery while pregnant during any trimester. However, the number of babies born with a birth weight < 1,500 and 2,500 grams, and the number of babies who died within 7 days of the operation was greater in those who underwent surgery while pregnant (Figure 1). This was true during all three trimesters. These risks could not be linked to either the specific anesthetic agents or the anesthetic technique. The increased risk to the fetus may be due to the condition that necessitated surgery in the first place, with the highest rate in gynecologic procedures. These data are important because they clearly demonstrate that anesthetic agents are not teratogenic and that the greatest risk is premature labor with the delivery of a low birth weight baby.

Behavioral teratology and Apoptosis in the newborn brain

In 1963 Werboff and Kesner[45] used the term behavioral teratology to describe the adverse action of a drug on the behavior of the offspring to its environment. It is well known that the halogenated agents particularly halothane and enflurane cause learning deficits in rodents.[46,47] Most anesthetic agents act by either blocking N-methyl-d-aspartate (NMDA) receptors or by enhancing GABA. Studies have demonstrated that when agents that act by either of these mechanisms (e.g., ketamine, nitrous oxide, midazolam, barbiturates and volatile agents) are administered to the rodent during the period of synaptogenesis, they induce widespread neuronal apoptosis in the developing brain.[48,49] Learning deficits have been described in the offspring of female rats exposed to commonly used anesthetic agents and widespread neurodegeneration was seen on histological examination.[50] The concern in the animal model extends beyond directly anesthetizing the animal but also anesthetizing the mother while she is pregnant. There are animal studies that demonstrate widespread apoptosis in the developing fetus and behavioral issues once born.[51,52] There are no human studies evaluating the developing fetus during non-obstetric surgery.

Although an association between anesthetic agents and neuronal apoptosis has been demonstrated in the animal model, extrapolation from animal studies to humans is problematic at best.[53] While most organ systems have completed development by the end of the first trimester or earlier, the brain continues to develop until after delivery. The time of greatest concern is during synaptogenesis or rapid growth spurt which is from the third trimester until three years of age. Randomized trials to confirm apoptosis in the human brain obviously cannot be done and evaluating effect of anesthesia on the brain is complicated. Recently, two separate authors assessed the effect of anesthesia and surgery on human behavior later in life. One looked at learning disabilities[54] and the other deviant behavior.[55] Both found an association between surgery and anesthesia and their outcome measures. The studies are far from conclusive as they were not randomized, and one was only a survey,[55] but they certainly highlight the need for well controlled studies.

The FDA has had multiple advisory meetings since 2007 to discuss the possible association between exposure to anesthetic agents and sedatives on human brain development. In December 2016 the FDA distributed an advisory that cautioned health care providers that repeated or lengthy exposure to general anesthetics and sedative agents may affect the development of children's brains and updated the package insert to reflect these concerns.[1]

The American College of Obstetrics and Gynecology responded to the advisory by emphasizing that all the studies on the effects of the fetal brain have been in the animal model and concluded that "no women should be denied a medically indicated surgery or procedure which may involve the use of these agents.[2] It is unclear if or how this advisory will affect anesthetic practice.

1 http://www.fda.gov/Drugs/DrugSafety/ucm532356.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery

2 http://www.acog.org/About-ACOG/News-Room/Statements/2016/ACOG-Statement-on-the-FDA-Warning-Regarding-Use-of-General-Anesthetics-Pregnancy

Avoidance of intrauterine fetal asphyxia

The most important consideration for the fetus during non-obstetric surgery is the maintenance of a normal intrauterine physiologic milieu and avoidance of intrauterine fetal asphyxia. Fetal oxygenation is directly dependent on maternal arterial oxygen tension, oxygen carrying capacity, oxygen affinity, and uteroplacental perfusion. It is therefore critical to maintain a normal maternal PaO_2, $PaCO_2$ and uterine blood flow.

General anesthesia is a particular risk to the pregnant woman because management of the airway can be difficult, and the rate of hemoglobin oxygen desaturation is increased due to the decreased functional residual capacity and increased oxygen consumption. Care must also be taken during a neuraxial anesthetic because a high dermatomal level of anesthesia, a toxic local anesthetic reaction, or oversedation can also lead to a hypoxic event. Elevated maternal oxygen tension commonly occurs during general anesthesia. Some have expressed concern that increasing the inspired oxygen level to the mother could be detrimental to the fetus by causing premature closure of the ductus arteriosus or retrolental fibroplasias. However, due to placental shunting of blood, fetal PaO_2 never rises above 60 mmHg even if maternal PaO_2 is 600 mmHg. Therefore, maternal inspired oxygen concentration should not be limited.

Both maternal hypercapnia and hypocapnia can be detrimental to the fetus. Severe hypocapnia produced by excessive positive pressure ventilation may increase mean intrathoracic pressure, decrease venous return and lead to a decrease in uterine blood flow. In addition, maternal alkalosis, as produced by hyperventilation, will decrease uterine blood flow by direct vasoconstriction, and it will decrease oxygen delivery by shifting the maternal oxyhemoglobin dissociation curve to the left. Severe hypercapnia is detrimental because carbon dioxide readily crosses the placenta and is associated with fetal acidosis and myocardial depression.

Uterine blood flow is affected by both drugs and anesthetic procedures. Placental blood flow is directly proportional to the net perfusion pressure across the intervillous space and inversely proportional to the resistance. Perfusion pressure will be decreased by hypotension which may be due to the sympathectomy from local anesthetics administered as part of an epidural or spinal anesthetic, from aorto-caval compression in the supine position, or from hemorrhage.

Prevention of premature Labor

Spontaneous abortions, premature labor and preterm delivery are the most significant risks to the fetus during maternal surgery,[1,2,36,37] It is unclear if this is due to the surgery, anesthetic or underlying medical condition, but the greatest risk is during gynecologic or pelvic procedures when there is uterine manipulation and the lowest risk occurs during the second trimester. The potent inhaled anesthetic agents decrease uterine tone and inhibit uterine contractions so from this perspective they may be beneficial. Also, medications that increase uterine tone such as ketamine at doses > 2 mg/kg should theoretically be avoided. No study, however, has ever documented that any particular anesthetic agent or technique is associated with a greater or smaller incidence of abortion or preterm labor.

Laparoscopic surgery

Once considered an absolute contraindication during pregnancy, laparoscopic surgery is now routinely performed.[56,57] Reedy et al.[58] compared five fetal outcome variables among pregnant women who had a laparotomy (n=2,181) versus those who had laparoscopy (n=1,522) between the fourth and twentieth week gestation, and the general pregnant population who did not undergo surgery. They found that there was an increased risk of preterm delivery and low birth weight (<2,500 grams) in both surgical groups as compared to the general population. But there was no difference in any of the other outcome variables between the two surgical groups.

Specific anesthetic considerations during laparoscopy include maintaining normocapnia because carbon dioxide is commonly used to maintain a pneumoperitoneum. Adjusting maternal ventilation to maintain end tidal carbon dioxide between 30 and 35 mmHg should avoid hypercapnia and fetal acidosis. The Society of American Gastrointestinal and endoscopic surgeons proposed guidelines for laparoscopic surgery during pregnancy (Table 4). Surgical concerns include caution during placement of the trochars which can be accomplished as an open technique and maintaining low pneumoperitoneum pressures (< 15 mm Hg) to maintain uterine perfusion.[59]

Fetal heart rate monitoring

Fetal heart rate (FHR) monitoring becomes feasible around 16-18 weeks with an external tocodynamometer, but the indication for its use intraoperatively is less well defined, and it obviously cannot be used in every case such as abdominal procedures. One issue is how to act on the information? If the fetus is not viable and the FHR tracing is concerning, all that can be done is normalize the physiologic milieu. Is this sufficient reason to use the monitor when

this should be done anyway? Katz et al.[60] reported a case in which they were able to correct an abnormal fetal heart rate in a woman who was undergoing eye surgery, by increasing the percentage of inspired oxygen given to the mother.

Another issue is who should interpret the tracing. Anesthetic agents will change the FHR baseline and decrease variability and these changes need to be distinguished from fetal compromise. Furthermore, if a change is noted and the fetus is viable will the obstetrician intervene with immediate delivery?

The American College of Obstetricians and Gynecologists issued a joint statement with the American Society of Anesthesiologists on this issue.[61] General guidelines from the statement include:

1. A qualified individual should be readily available to interpret the FHR.
2. If the fetus is below a viable gestation, it is generally sufficient to ascertain the FHR before and after the procedure, but that in "select circumstances" intraoperative monitoring may be considered to facilitate positioning or oxygenation interventions"
3. If the fetus is viable then simultaneous FHR and contraction monitoring should be considered intraoperatively and an obstetric provider should be available and willing to intervene for fetal indications

The statement concludes by stating, "the decision to use fetal monitoring should be individualized"… and "ultimately, each case warrants a team approach for optimal safety of the woman and fetus".

General Recommendations for anesthetic management

Whenever possible, anesthesia and surgery should be avoided during the first trimester. Although no anesthetic drug has been proven teratogenic in humans it is prudent to minimize or eliminate fetal exposure during this period of organogenesis if at all possible.

Prior to initiating any anesthetic an obstetrician should be consulted and fetal heart rate tones should be documented. Precautions against pulmonary aspiration by the mother should be taken from as early as the 12th week and a clear non-particulate oral antacid administered and H_2 receptor blocker and metoclopramide considered.

Apprehension should be allayed by reassurance from the anesthesiologist rather than with premedication, if possible. The patient should be informed that there is no known risk to the baby regarding congenital malformations but that there is an increased risk of abortion or premature labor. This is a good opportunity to educate the patient as to the signs of premature labor, e.g., back pain in someone prior to term, which can occur up to one week after the procedure. The patient should be transported to the operating room with left uterine displacement to avoid aorto-caval compression after 16-18 weeks gestation.

In addition to the standard ASA intraoperative monitors, the fetal heart rate and uterine tone should be monitored, if at all possible. It is the best way to assure maintenance of a normal physiologic milieu for the baby. Monitoring and interpretation should be performed by an obstetrician or someone other than the anesthesiologist with expertise in FHR interpretation. Regardless of the decision to perform intraoperative FHR monitoring, the FHR and uterine contractions should be monitored before and after the surgery.

The type of anesthesia should be based on maternal indications, the site and nature of the surgery, and the anesthesiologist's experience. Because MAC is decreased, the dose of all anesthetic agents for regional or general anesthesia should be reduced. Although no study has found any difference in neonatal outcome in terms of congenital defects or preterm delivery, regional anesthesia may be preferable to general anesthesia to avoid the risk of pulmonary aspiration and decrease fetal drug exposure.

The largest risk of neuraxial anesthesia is hypotension, which may reduce uteroplacental perfusion. Prevention is difficult since prehydration does not reliably reduce the incidence of hypotension. If hypotension occurs, ephedrine or phenylephrine can be used. The key is not which drug is chosen but that hypotension should be recognized and treated quickly.

General anesthesia should be preceded by careful evaluation of the airway, denitrogenation, and a rapid sequence induction with the application of cricoid pressure. Edema, weight gain and increase in breast size may make laryngeal visualization and tracheal intubation technically difficult. An array of laryngoscope blades and handles, and other emergency airway management equipment should be available. Capillary engorgement of the mucosal lining of the upper airway accompanies pregnancy. This mandates extreme care during manipulation of the airway and the use of a smaller-than-usual endotracheal tube. The use of a nasal airway and naso-tracheal intubation should be avoided to eliminate the risk of nasal hemorrhage. A high inspired concentration of oxygen should be used (at-least 50%) and arterial pCO_2 should be maintained at normal pregnancy levels (30-35 mmHg). End-tidal CO2 is an excellent

approximation of paCO2 in the pregnant patient because the arterial-to-end-tidal CO2 gradient decreases during pregnancy.

Fetal heart rate and uterine activity monitoring should continue postoperatively. Epidural or subarachnoid opioids are an excellent choice for pain management because they cause minimal sedation and smaller doses can be utilized compared to the intramuscular or intravenous routes. Non-steroidal anti-inflammatory drugs should be avoided because they may cause premature closure of the ductus arteriosus.

Conclusion

Non-obstetric surgery during pregnancy is common and can be provided safely as long as certain principles are adhered to. The greatest risk to the mother centers around the airway and avoidance of hypoxia. The greatest risk fetus is preterm labor and delivery and not congenital defects. Regardless of the technique, attention to detail and maintenance of a normal intra-uterine physiologic milieu throughout the perioperative period, including the avoidance of hypotension, hypoxemia, hypercapnia, hypocapnia, hypothermia and acidosis, is the key to a successful outcome.

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ANESTHESIOLOGY 2017
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Spinal Cord And Dorsal Root GanglionStimulation

Timothy R. Deer, MD **Charleston, West Virginia, USA**

INTRODUCTION

It is an exciting time to discuss Spinal Cord Stimulation (SCS), Dorsal Root Ganglion Stimulation (DRG), and new innovations in our field. Innovation is taking place in Europe, Latin America, Asia, Africa, Australia, and the United States. New long term data is being gathered on comparative studies, new devices and new ways to signal the nervous system. New computer spine interfaces are changing the way we neuromodulate. This talk will give an overview of these new developments and discuss the next generation of studies that are on the horizon.

THE SAFE PRINCIPLES

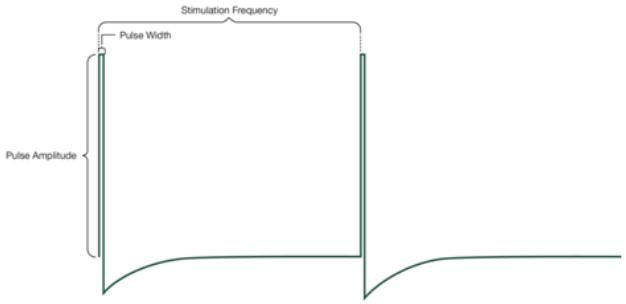
New therapies should be carefully vetted as to efficacy and safety. As we discuss each new option we should also take a critical look at the overall impact on the field. This can be done based on a published analysis. The introduction of the SAFE algorithm should be applied to these techniques. This is an acronym for the requirements that should be applied to interventional treatments: they should be relatively safe, appropriate, fiscally neutral and efficacious. As I discuss each issue we will examine any deficiency in these areas.

OVERVIEW OF TRADITIONAL OR TONIC STIMULATION

THE PROCEDURE AND THE SCIENTIFIC PRINCIPLE

Implantation of a SCS system is performed when determined to be medically necessary and indicated based on patient charateristics, mechanical features of the spine and algorithmic thought. Once planned the procedure occurs in two stages; a temporary implant which allows the patient to evaluate their response to the therapy and a permanent implant in which both stimulating electrodes are placed over the spinal target and then connected to an implanted programmable computer and power source. By using a programmable generator, the amplitude, rate, pulse train, frequency and shape of the electrical field can be manipulated to create pain relief and change other electrophysiological features of the body. The mechanism of neural effect has been theorized to change the balance of inhibitory to excitatory fiber activity by the gate control process, which is determined by the shape of the electrical field determined by the electrodes. Recently new software and devices has led to new theories of mechanisms including impact on the C fibers, A beta fibers, wide dynamic range neurons, and the medial and lateral thalamus. Conventional stimulation involves a tonic waveform with frequency usually being delivered between 40 and 100 Hz. (figure 1). This current creates a parasthesia that results in a “pacing” type sensation that many patients find to be pleasant and often creates pain relief. In previous discussions we have often concluded that to reduce pain, most scientists believed the parasthesia must cover the dermatomal pattern of pain. With new waveforms, pulse trains, frequencies and targets, this theory now does not appear to be accurate in many clinical settings. The tonic wave form is seen in figure 1.

Figure 1. Tonic Waveform



LOGICAL PROGRESSION OF PAIN TREATMENT

The algorithmic treatment of pain is currently the standard of care for improving pain levels, function, and quality of life. In recent years, many experts have recommended the use of SCS much earlier in the algorithm; namely before a second spine surgery in neurologically stable patients, before chronic opioids in patients with mixed or neuropathic pain, and in some cases prior to the first back surgery in patients with multi-level disease or uncertain surgical outcomes. The change in the algorithm is due to several factors including the simplification of stimulation trialing, improvement of programming, and diversity of arrays and frequencies. Evidence based medicine also is favoring SCS over other strategies, shown nicely in three randomized studies with primary investigators Kapural, Deer and Levy. Kapural and colleagues showed superior pain relief of HF10 over conventional SCS. Deer and Levy led the ACCURATE study, which showed superiority of DRG stimulation as compared to tonic stimulation for nerve pain of the groin and lower extremity. Deer, Slavin, Staats and North led a study that showed superiority of the Burst waveform as compared to tonic stimulation with the patient as a self control. Recently Thomson and colleagues presented a new prospective study looking at many different frequencies with the patient blinded to the therapy. In this International study pain relief was seen in each group with the patient blinded to the treatment arm. In another prospective effort, Russo and colleagues in Australia showed efficacy and safety in a group of patients with intractable back and leg pain using a new closed loop feedback system.

In addition to improved evidence the desire to avoid opioids and addiction is leading to an interest in these methods. This is leading to increased investment, research, and development of new devices.

INDICATIONS AND PATIENT SELECTION:

In the United States, the FDA has approved this therapy for the treatment of moderate to severe pain in the trunk or limbs. The specific indications for which these devices are most commonly used have been well defined. The most common indication for spinal cord stimulation is failed back surgery syndrome. Other common reasons patients undergo these surgeries include radiculitis, complex regional pain syndrome, peripheral neuropathies, post herpetic neuralgia, ischemic limb pain, angina, pelvic pain and other neuropathic and visceral pain syndromes. In recent months we have published the results of a pain registry that lends further support to the use of SCS in the cervical spine to treat diseases of the head, neck and upper extremities.
A recent consensus group, the Neuromodulation Appropriateness Consensus Conference (NACC), has commented on proper uses of SCS for neuropathic pain, vascular diseases and angina. The NACC has also published on contraindications and improving safety. These papers will be an important guide for patient safety. Recently new recommendations have been published in an evidence based fashion with insights on reducing infection and bleeding. These papers, The NACC 2017, will hopefully lead to improved outcomes and better patient efficacy.

SPINAL CORD STIMULATION: THE PROCEDURE

GENERAL PRINCIPLES

After appropriate patient selection and education the patient should undergo preoperative evaluation for perioperative risks. Once cleared for trialing, the patient should be interviewed by the anesthesiologist and stabilized. Preoperative antibiotics are based on local pathogens and susceptibilities. Most common antibiotics include intravenous vancomycin or a third generation cephalosporin preoperatively, bacitracin or kantrex, intraoperatively. Intraoperative prepping and draping should be broad and extend well beyond the surgical field. Positioning should facilitate surgical technique and patient safety and comfort.

IMPLANT METHOD

The use of a percutaneous lead or surgical paddle lead is at the discretion of the implanting physician. Percutaneous leads are introduced in a less invasive and less dangerous method so are usually preferable, but in some cases, such as those with complex spinal disease, extensive scar tissue, or primary axial back pain a paddle lead may be a better choice. In those who obtain a percutaneous lead, whether using a cylindrical lead or new paddle constructs, a needle must be placed appropriately prior to delivering the device. New needle constructs have been developed over the past year and will be discussed during this session.

NEEDLE PLACEMENT

Prior to implanting a device physicians should consider planning the needle placement including the level of entry, the side of entry and the angle. In the lumbar spine needles are usually placed into the epidural space at 30 to 45 degrees. A paramedian approach is preferred, with a skin entry site one and half to two levels below the desired entry space. The needle entry into the epidural space should be two to three levels below the final lead target. In the cervical spine the needle entry should be below the T1 vertebral level. Lead placement for DRG stimulation is paramedian and contralateral. The angle for proper needle placement will be shown and discussed in this session.

LEAD PLACEMENT

Lead placement has evolved in recent years. Classically the lead is placed into the posterior epidural space and confirmed on AP and Lateral fluoroscopy. The targets are noted in the tables below. DRG targeting also also been mapped and is shown in Table 2.

EPIDURAL LEAD TARGET

The physician should understand the target for the led to achieve proper stimulation. Table 1 provides general targets for spinal cord stimulation.

DRG stimulation is mapped somewhat differently since the target is at the level closest to the impacted dermatome. DRG stimulation also has the major advantage of divergence and convergence at the spinal level, which allows the clinician to stimulate the DRG at a level that may be within 2 to 3 levels from the area of the pain generator.

Table 1. Lead Placement for Tonic Stimulation

Region	Position	Target
Cervical	C2 Lateral	Mandible, Neck, Shoulder
	C2-3	Shoulder, Arm
	C4-6	Arm, Hand
	C7-T2	Anterior Shoulder, Chest
Thoracic	T3-T6	Abdominal, Thoracic, Visceral Organs
Thoracic	T1-3	Angina, Chest
	T4-6	Visceral Abdomen
	T7-9	Axial Back
	T10	Knee, Hip
	T11-12	Leg, Foot
Lumbar	L1	Foot, Possible Pelvic Organs
	L5-S1 Nerve Root	Foot
Sacral	S2-4	Pelvis, Rectum, Perineum

Table 2. DRG mapping.

Jeff, Please insert table from slide here.

LEAD PROGRAMMING

The field of stimulation or the array is influenced by the number of the cathode (negative) and anode (positive) electrodes and the orientation of each contact. Current is driven into the neural tissue based on the presence of a cathode. The optimal current delivery occurs when a cathode is surrounded or "guarded" by an anode on each side. New lead arrays have been developed using percutaneous, percutaneous paddle and paddle leads. Cross talk between leads, program cycling and isolated electrode programs may impact the outcomes. Programming for DRG, Burst and HF 10 requires a new skill set and physician and nurse training to these new methods will be important.

LEAD ANCHORING

In analysis of complications of SCS, the possibility of lead movement is always a major concern. The advent of new "mechanical" or locking anchors has reduced this problem. Other factors appear to be moving the anchor into the ligament, angle of needle entry, and suture methods. Making an incision into the ligament around the needle prior to removal may allow the new longer mechanical anchors to slide into the ligament and reduce the strain on the materials that may reduce migration. Paddle implants have less migration, but that must be balanced against the difficulty of revising the lead, lead fracture and the increased risk of major neurological deficits. DRG leads appear to have less necessity for anchoring due to epidural slack, which is a technique that is incorporated into training.

POCKET FORMATION

The position of the pocket is based on patient preference and body habitus. Options include the buttock, abdominal wall, flank, and chest wall. The depth of the pocket should be appropriate to avoid skin erosion, but should also assure good communication with telemetry. The implanter should consider sleeping patterns, shoulder mobility and patient clothing preferences when planning the pocket. Some new wireless devices do not have an internal generator and do not require a pocket. The use of external power sources is an engineering challenge.

COMPLICATIONS OF SCS

The most common complications of spinal cord stimulation include lead migration, superficial infection, impedance abnormalities, post dural puncture headaches, and nerve irritation. More serious problems include epidural hematoma, epidural abscess, paraplegia, and death. The NACC papers look at each of these problems and discuss possible ways to mitigate complications. Best practices should reduce these complications.

INNOVATIONS IN STIMULATION OF THE CENTRAL NERVOUS SYSTEM

STIMULATION OF THE DORSAL ROOT GANGLION

The anatomy of the DRG makes it an attractive target for neuromodulation. The structure is a sensory neural body that contains the soma from primary sensory neurons. The ganglion is located within the bony structure of the spine just below the pedicle where it reliably lies in all patients, and both transmits and influences sensory neural impulses traveling from the periphery. The ganglion contains multiple cell types including neurons and glial cells that change and become hyperexcitable in chronic pain conditions. (Figure 2, with permission of Jeff Kramer, PhD) The DRG has been a target for injection, surgical interventions and radiofrequency in the past, but with no long-standing efficacy. The development of new novel leads, delivery tools and multi-channel generators has led to the use of DRG stimulation as a major advance in the treatment of intractable pain syndromes. The lead shape allows for selective stimulation of the DRG without encompassing the surrounding structures. (Figure 3) The multi-center prospective randomized study, The Accurate study, has been published in the journal Pain. This study showed superiority of DRG stimulation to SCS in the population studied which was patients with nerve injury below the waist and those with classic Complex Regional Pain Syndrome. Figure 4 shows the pivotal primary endpoint.

Figure 2. The presence of hyperexcitable fibers in the DRG appears to lead to selective stimulation of the abnormal areas of the pain transmission and avoids the over stimulation of fibers that may lead to motor stimulation.

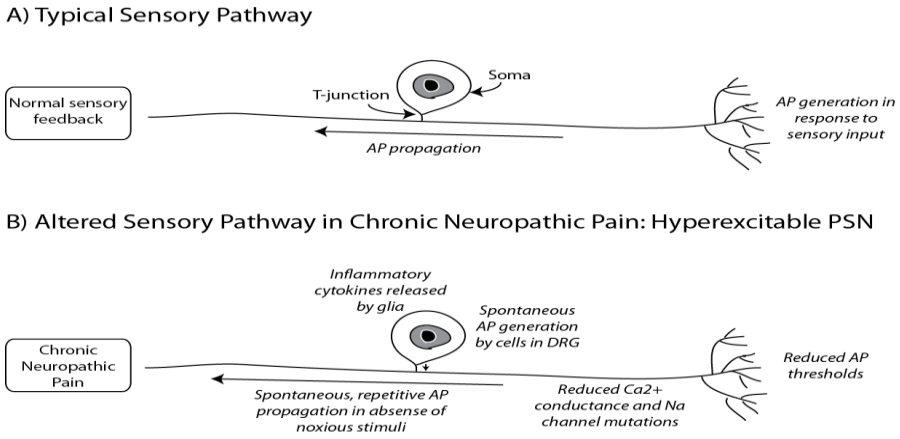


Figure 3. Lead Placement

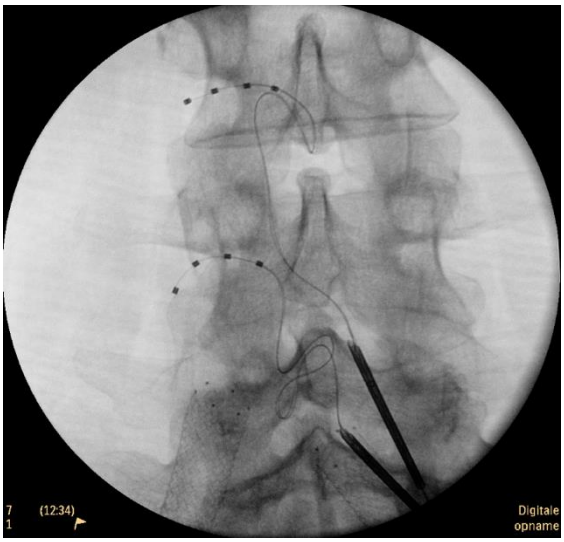


Figure 4.

Jeff please insert Figure 4. Results of DRG Accurate study.

HIGH FREQUENCY METHODS OF SCS

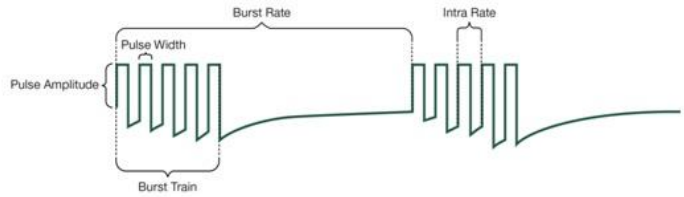
Until the past few years, low frequency has been standard in clinical neurostimulation. It has been rare for patients to be treated with frequencies greater than 100 Hz. Work done in the United States, Europe and Australia has suggested that the use of High Frequency Stimulation (HFS) may give significant relief in those who have primary axial back pain, cervical pain, or complex patterns or those with inability to tolerate the feeling of parasthesia with conventional stimulation. HFS involves the use of leads, similar to conventional systems, placed based on anatomical strategies noted above. The frequency used in these devices approach 10, 000 Hz, but may also be used to deliver more standard frequencies. Recent work on using 5,000 Hz did not show efficacy suggesting that the higher frequency may be more efficacious. A recent study by Thomson and colleagues showed equal analgesic response to 1K, 4K, 7K and 10k in a multicenter prospective fashion. This study called the Procor study was presented in Scotland at the INS meeting in 2017. Figure 5 shows a representation of a typical HFS waveform.

Figure 5 – High Frequency Waveform 10,000 Hz

BURST DeRidder STIMULATION

The use of tonic stimulation in both high and low frequency ranges have shown good outcomes in thousands of patients. Work by DeRidder and colleagues have suggested using rapid non-tonic bursts of high frequency signal rotated with periods of electrical silence to produce pain relief without parasthesia. This concept has great potential to salvage those failing traditional low frequency tonic stimulation and is attractive that using the same generator you could use both tonic and burst stimulation to optimize outcomes. A recent multi-center prospective comparative study showed improved efficacy with the burst waveform as compared to tonic pulse trains. Scientific work has shown a dissociation of pain response and suffering. This dissociation may lead to improved function and reduction of other treatments including opioids. Figure 6 shows an artist rendering of a burst waveform.

Figure 6. Burst Waveform



CONDITIONAL APPROVAL OF MRI

At the time of this lecture all commercial devices have some ability to undergo an MRI. Some devices have indications for the brain or limbs only, while others have total body. The implanting doctor should weigh the ability to obtain a good outcome verses the need for an MRI and personalize patient care.

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CLOSED LOOP AND FEEDBACK MECHANISMS

Recent work in Australia showed that a device with feedback loop technology can improve the amount of pain relief in a open label fashion with back and leg pain treatment . This study, called the Avalon study was presented by Russo at the INS meeting in Scotland in 2017. An United States study has began to obtain FDA approval. This study, called the Evoke study, is a multi-center, double blinded prospective, randomized, comparative study to access efficacy and safety. This technology involves real time spine computer interfaces to change the computerized electrical delivery based on Evoked Action potentials.

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Pediatric sedation: methods to enhance safety

Jerrold Lerman MD, FRCPC, FANZCA **Buffalo/NY**

During the past 25 years, pediatric sedation has grown exponentially to facilitate the completion of many medical and minor surgical procedures outside of the operating room. This growth has involved a broad range of sedatives that were administered in both traditional and non-traditional settings such as dental offices, gastrointestinal clinics and radiation units, by anesthesiologists as well as non-anesthesiologists including intensive care and emergency physicians to children who presented with a host of medical conditions and who were monitored to varying degrees. To assess the risk of serious adverse outcomes in these units, data from several extensive databases and case reports together with data from randomized studies have painted a clear impression of the severity of the risk of sedation. When qualified and trained providers delivered sedation, the frequency of serious adverse events was small, and non-life-threatening. However, serious events have occurred during sedation (as in the well-known cases of Michael Jackson and Joan Rivers) that for the individual has been irreversibly devastating. Eighty percent of serious adverse events during sedation are respiratory in origin.[1] Respiratory events in closed claim reports of sedation in patients of all ages occurred twice as frequently outside the operating room (O.R.) as in the O.R. with inadequate oxygenation/ventilation occurring 7 times more frequently outside the O.R. than inside and twice as frequent in children <16 years outside the O.R. (11%) versus inside (6%).[2] In the gastroenterology unit, data from the pediatric sedation research consortium revealed an overall frequency of 4.8% adverse events, with no deaths or cardiac arrests but persistent desaturation (1.5%), airway obstruction (1%) and laryngospasm (0.6%) in >12,000 procedures.[3] Serious adverse events occurred in 15% of infants, 8% of children and 4% of older children.[3]11 In the emergency department, a meta-analysis of studies with ketamine sedation highlighted age (<2 yr or > 13yr), large doses of ketamine and co-administration of anticholinergics or benzodiazepines as factors that increased the risk of acute airway/respiratory events.[4] In the dental office, sedation in children 2-5 years was associated with the greatest risk of death, with spotty monitoring a contributing factor.[5,6] Such events should not occur to these extents and I hope you hear in this lecture will help you avoid experiencing similar adverse events in your practices.

In an effort to standardize the quality of sedation delivered and optimize outcomes, protocols and guidelines have been developed under the aegis of several national organizations. This lecture addresses a number of controversial issues that relate to pediatric sedation including:

1. What level of sedation is required?
2. Who can provide sedation?
3. Which skills are required to safely deliver sedation?
4. Infrastructure
5. Preoperative assessment of the children
6. Monitoring
7. Which sedatives?

Sedation levels.

Sedation is a continuum from wakefulness to general anesthesia. Although discrete levels of sedation have been carefully defined, children who are sedated may drift from one level of sedation to another and back, depending on the doses of sedatives administered, age of the subject, pre-existing medical conditions and over time. As a result, the provider must be prepared to manage a level of sedation deeper than the target level including intervening for cardiopulmonary resuscitation and potential serious adverse events that may ensue. The varied terminology for these levels of sedation has been revised recently with the following result:[7]

Minimal sedation: anxiolytics permit the child to respond to verbal commands; cardiorespiratory responses are maintained.

Moderate sedation: sedatives permit the child to respond to verbal commands or to light, tactile stimulation; cardiorespiratory responses are maintained.

Deep sedation: consciousness is not maintained; responds to painful or repeated verbal stimuli; spontaneous respiration may be inadequate and require support, the airway may become obstructed and reflexes attenuated; cardiovascular responses may be maintained or require minimal support.

General anesthesia: an unconscious state in which painful stimuli fail to arouse the child; respiration may be spontaneous but diminished in frequency or depth, although apnea is common; cardiovascular responses may require support.

The level of sedation required depends on the intended procedure and the level of pain associated with it (MRI without pain but no movement versus bone marrow biopsy with pain preferably no movement), age of the child, level of cooperation and co-existing diseases.

Who can provide sedation?

Sedation has been administered by anesthesiologists, intensivists, emergency medicine doctors and pediatricians. Evidence suggests that the frequency of serious adverse events with sedation by all of these providers is similar.[8] Healthcare providers (both physicians and nurses) who may provide sedation to children should maintain pediatric advanced life support credentials with skills in recognizing compromised respiration and circulation; in intervening to re-establish a patent airway and stable circulation using facemask/positive pressure ventilation as well as advanced airway skills as needed for greater depths of sedation. In the latter case, having providers with the skills to insert an LMA or intubate the trachea is preferred, although an airway expert (anesthesiologist) in the immediate vicinity may suffice. Maintaining skills for sedation providers may be challenging as rare events (eg., laryngospasm) do not permit ongoing exposure to maintain those skills, resulting in loss of skills. Sedation providers may rotate through the operating room to maintain their skill levels in airway management; in addition, simulated scenarios may be helpful.[9] In general, the minimal level of training to establish a skill set for a particular maneuver (eg., laryngoscopy) ranges from 50-100 successful attempts depending on the study design. [10,11] However, there are a number of tricks to extricating the obstructed airway that are not widely appreciated (since most instrument the airway with some device in pediatric anesthesia today) and these will be reviewed and emphasized in this lecture).

Which skills are required to safely deliver sedation?

Delivery of a specific level of sedation requires the skills to manage a deeper level of sedation than anticipated since patients not infrequently drift to deeper levels of sedation than targeted. The primary concerns that may lead to serious adverse events from sedation relate to airway issues: apnea, partial airway obstruction and laryngospasm. These occur with greater frequency with deeper levels of sedation (deep sedation) and ASA P/S 2 and 4 children.[12] The spectrum of skills required to identify abnormalities in respiration include basic observation of chest wall movement (is the child breathing? Is the chest wall moving? Is there evidence of upper airway obstruction-supraclavicular, suprasternal retractions?), vigilance of monitors (what is the oxygen saturation and capnogram?) and auditory cues that an alarm has sounded (desaturation pitch from the oximeter).

Adequate oxygenation in the child with normal cardiorespiratory function can usually be maintained by administering an exogenous source of oxygen (via nasal prongs or a facemask) providing the child is breathing.

Adequate ventilation on the other hand, may be more challenging as no exogenous source of gas can maintain ventilation: for the most part, at all depths of sedation short of general anesthesia, spontaneous respiration with or without support, is required.

Partial airway obstruction may be manifested by a degree of oxygen desaturation, a blunted capnogram and/or paradoxical chest wall movement. If the oxygen saturation is maintained >92% (depending on the severity of existing pulmonary disease), it is unlikely that oxygenation is a serious concern. However, when the oxygen saturation decreases to less than 90%, an intervention is required as the rate of desaturation may accelerate rapidly particularly if the airway has become completely obstructed. Several maneuvers may be applied to relieve the airway obstruction including insertion of an Oropharyngeal airway, a nasal pharyngeal airway, repositioning the head/neck, extension of the neck and a jaw thrust maneuver. This practitioner focuses primarily on repositioning the head/neck as needed and the jaw thrust maneuver to relieve airway obstruction. Proper application of the jaw thrust maneuver is not widely taught because most apply an incomplete maneuver by applying jaw thrust at the angle of the jaw rather than the condyle of the ascending ramus of the mandible.[13] This maneuver not only relieves supraglottic airway obstruction, but during all levels of sedation except general anesthesia, is a painful stimulus that may trigger movement of the extremities or head/neck.

Infrastructure.

Sedation should not be administered in the absence of a source of oxygen, suction and scavenging (should nitrous oxide or other inhaled agents were used). In addition to these minimum requirements, an acronym known as SOAPME highlights the equipment that should be immediately available for all sedation cases: [14]

S is for size of appropriate suction catheters and equipment (including a Yankauer)
O is for oxygen source including flowmeter and control valve
A is for appropriate airway (oral or nasal) including facemask, oral and nasopharyngeal airways, LMA, laryngoscope blades and tracheal tubes.
P is for pharmacy to ensure an adequate supply of the much needed sedative/analgesic drugs and resuscitation drugs.
M is for monitors including age appropriate oximeter and blood pressure cuff, electrocardiogram, end-tidal pCO_2 and precordial stethoscope. Temperature monitoring should be available.
E is for special equipment/drugs (eg., defibrillator)

A proper preoperative record, sedation chart (paper or electronic) and postoperative recovery form should be available. Discharge criteria should be standard recovery room discharge criteria.

Often overlooked, is access to a resuscitation room in the vicinity of the sedation site. This is of particular importance in the MRI radiology suite, where a child who arrests must be extricated from the vicinity of the magnet and resuscitated in a room in which full resuscitation equipment including defibrillator is immediately available. Most areas of the hospital including most sedation locations have resuscitation equipment immediately available but it is wise to be familiar with their location.

Preoperative assessment of the children.
Children should be prepared for sedation/anesthesia in the usual manner as per ASA guidelines. Most children being ASA P/S 1 or 2 do not require specific preoperative testing (other than pregnancy testing in females who are menstruating). Children who are ASA P/S 3 or 4 may require preoperative testing depending on pre-existing diseases (eg., ECHO for a child with congenital heart disease). Children with severe OSA and ex-premature infants <60 weeks post-conception age may require careful choice of medications (such as the dose of opioids if nocturnal desaturation was reported in the child with OSA) or a period of prolonged observation or elective admission postoperatively until they are no longer at risk for postoperative adverse events. Children with obesity, Down syndrome and myopathies (including MH) must be carefully evaluated for their suitability to undergo sedation in a remote site and the need for admission as the frequency of severe adverse events, particularly airway events, in these children is substantive.[15,16]

Managing children with malformations of the airway in remote sites is discouraged. There is no clear standard for managing such airways and performing procedures in these children in the O.R. where difficult intubation equipment and assistance is readily accessible. Having said that, using difficult intubation equipment that are not MRI compatible in the MRI unit and other locations that have limited space poses a challenge for providers/sedationists that in an emergency could prove disastrous. Each case should be evaluated on an individual basis, in concert with the team of care providers and family to ensure a satisfactory outcome is achieved.

All children who present for elective sedation should be fasted based on standard fasting guidelines. In the case of emergent cases (eg., sedation in the ED) there is no known time interval between eating and the accident that would reduce the risk of regurgitation and aspiration to elective levels. Such children may best be managed by tracheal intubation to reduce the risk of pulmonary aspiration. Interestingly, fasting data from a large sedation database demonstrated that the fasting interval was not a major determinant of the risk of regurgitation and aspiration.[17] This may be attributed to many reasons and for now, we abide by standard fasting intervals whenever possible.

A complete history and physical examination must be documented, including ongoing medical conditions, past anesthetic difficulties, documented allergies to medications (and latex), and a family history of untoward anesthetic complications must be assessed and documented. Physical examination should focus on the key elements for anesthesia including the airway, respiratory and cardiovascular systems. Since most airways remain non-instrumented for the sedation, care must be taken to ensure that with proper positioning a patent airway is possible. Informed consent (written or verbal according to local practice) that outlines the risks, benefits and alternatives to the parents, emancipated minor or consenting teenager should be obtained before commencing the sedation the sedation.

Monitoring.
Essential monitors for all level of sedation/anesthesia include electrocardiogram, blood pressure, pulse oximeter, capnometer and temperature. Supplemental monitors may include a depth of anesthesia monitor and a nerve stimulator, the latter if muscle relaxants are administered.

Each monitor contributes a discrete piece of information that may help to appreciate the overall state of the subject. An electrocardiogram is essential to not only document the heart rate, but to also identify arrhythmias should they occur. Failure to apply an electrocardiogram could delay the diagnosis and treatment of a serious arrhythmia. Pulse oximeters can measure the heart rate but cannot display rhythm disturbances. However, pulse oximeters measure the hemoglobin oxygen saturation, NOT hypoventilation, as any supplemental oxygen will delay detecting hypoventilation and apnea,[18] rendering the oximeter a second-line monitor of disturbed ventilation. Capnography, a display of the pCO_2 waveform, is a true monitor of ventilation. Indeed, evidence indicates that capnography detects the early onset of apnea (4.4 min before hypoxia)[19] and reduces the frequency of desaturation by almost 50%.[20,21] Ideally, we would prefer to monitor changes in tidal volume as diminution in tidal volume precedes apnea but there are no monitors currently available to provide such metrics, although a number are under development.[22,23]

Which sedatives?

New sedatives and anesthetics have completely written the prescription for sedation in children over the past three decades.[24] Early sedatives primarily used by nursing and non-anesthesiologists included midazolam, fentanyl, pentobarbital and chloral hydrate. In children 0.1 mg/kg midazolam has an onset of 1 minute and a maximum effect by 3-5 minutes. It is metabolized by CPY3A4 with a duration of action of 30-60 minutes. It may be infused for prolonged sedation but its context sensitive half-life increases with the duration of the infusion. One important advantage of midazolam is that it may be antagonized using flumazenil, 20 mcg/kg IV. Fentanyl is a short-acting opioid that provides mild sedation and analgesia, but is a powerful respiratory depressant. Like midazolam, it too can be antagonized with naloxone (20 mcg/kg). Pentobarbital and chloral hydrate as infrequently administered by anesthesiologists, but they have provided adequate sedation in infants and young children. We provide dental sedation in our dental clinic for single tooth and molar extractions in cognitively impaired children. We compared oral and intranasal midazolam, intranasal midazolam combined with oral transmucosal fentanyl citrate and intranasal midazolam combined with intranasal sufentanil.[25] All four sedatives were equally effective, yielding a 73% success rate. Ketamine is widely used for sedation in the emergency department. It is an effective anesthetic/sedative/analgesic with a small frequency of serious adverse events,[26] but is associated with increased postoperative nausea and vomiting. A very different profile of drugs have been used to sedate children in dental offices for molar extractions and other minor dental surgery including intranasal dexmedetomidine,

Serious adverse events have been associated with the administration of multiple sedative concurrently, nitrous oxide and younger children.[27] Ketamine has been associated with laryngospasm and cardiac arrest in several studies conducted in the emergency department.[28]

The newer agents propofol and dexmedetomidine have supplanted many of these older medications for sedation. In the case of propofol, it has a rapid onset of action, rapid offset and large clearance, greater than liver blood flow. It has a long terminal elimination (3-9 hours) which may lead to a slower emergence after a prolonged infusion (increased context-sensitive half-life with decreasing age).[29] Propofol doses (1-4 mg/kg) IV induce anesthesia and may be followed with an infusion. The rate of the infusion in children is 150-300 mcg/kg/min (9-18 mg/kg/h) for most procedures. For MRIs, children 1-8 years of age usually require 250-300 mcg/kg/min (after a mask sevoflurane induction) to remain still; smaller doses will result in movement. The infusion requirements are greater in younger infants and those who are cognitively impaired; in some cases, the rate may have to be increased temporarily to 400 mcg/kg/min to prevent movement. To ensure success in these scans, a shoulder roll to extend the neck is mandatory lest upper airway obstruction occurs. Propofol may cause transient apnea after a bolus dose particular if co-administered with other sedatives; reduces the dimensions of the upper airway similar to dexmedetomidine in children with OSA.[30] Propofol infusion syndrome is a rare complication that has not been reported in children undergoing procedural sedation. There is no drug to antagonize the sedative effects of propofol.

Dexmedetomidine is an $alpha_2$ agonist agent with much greater affinity for receptors than clonidine. It is not commonly used for sedation in children because it is quite costly in most US institutions. Loading doses of 1 mcg/kg following by an infusion of 0.7 mcg/kg/h may be used to sedate children, although it is infrequently used as the sole agent as children do not remain still with this dose. Unlike propofol, dexmedetomidine does not burn upon IV administration. Either larger doses of dexmedetomidine such as 2-3 mcg/kg/h and an infusion of 1-2 mcg/kg/h[31] or an adjunct agent such as midazolam 0.1 mg/kg must be given to prevent movement during dexmedetomidine sedation for MRI.[32] This drug may cause hypotension and bradycardia (frequency 3%)[33] (avoid anticholinergic agents, use ephedrine to treat bradycardia and hypotension), although its main advantage is that it neither depresses

respiration nor reduces the dimensions of the upper airway. Recovery after dexmedetomidine is slower than that after a comparable dose of propofol for MRI.[32,34]

Novel sedatives continue to evolve. Although some may reach phase 3 clinical trials, most remain in development, unavailable for clinical use. We shall conclude with a brief look at possible future sedatives for our armamentarium.[35,36]

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Current Controversies in Adult Outpatient Anesthesia

Jeffrey L. Apfelbaum, M.D. **Chicago/Illinois**

Introduction

The world of ambulatory anesthesiology continues to present anesthesiologists with a rapidly changing array of challenges, particularly as we continue to focus on quality and safety issues in this face-paced environment. This Refresher Course will provide an update on current controversial issues in adult outpatient anesthesia, including fast tracking; preoperative assessment, evaluation, and preparation; RN administered propofol sedation; the paradoxical relationship between obesity and risk in patients undergoing non cardiac surgery; and the current status of a new paradigm (computer assisted personalized sedation or CAPS) of moderate sedation for our patients. Additionally we will consider a variety of "breaking news" areas of controversy which may include topics such as advances in and recommendations to enhance perioperative communication; treatment decisions for patients on beta blockers and those with coronary artery stents; opportunities to incorporate one's personal outcomes data into your patient care plan and the potential effect of choice of anesthetic on cancer recurrence rates.

Fast Tracking: Eliminating Intensive Post-Operative Care in Same Day Surgery Patients Using Short Acting Fast Emergence Anesthetics

Many anesthetics have the pharmacokinetic and pharmacodynamic advantages of a shorter duration of action and a more rapid rate of recovery that permit a faster emergence from anesthesia compared with their predecessors. Less than 30 years ago, it was unthinkable that patients would be able to return home on the day of surgery. Today, advances in surgery and anesthesiology make it routine to perform the vast majority of all surgical procedures safely and effectively on an ambulatory basis, with many patients ready to be reunited with their families within minutes of emergence from anesthesia. In today's cost sensitive healthcare environment, the processes of ambulatory surgical care must be continually re-evaluated to take advantage of advances in technology and pharmacology and to optimize efficiency of the ambulatory surgical care without detriment to patient safety or satisfaction.

Traditionally, ambulatory surgical patients go from the operating room to the postanesthesia care unit (PACU) or recovery room (a highly specialized intensive care unit) for their immediate postoperative recovery from anesthesia and then to a second stage recovery unit (SSRU) for preparation for home readiness. By its very nature as a specialized ICU, the PACU is an expensive, labor-intensive environment. After a set of recovery criteria [1, 2, 3] are met in the PACU, the patient is usually transferred to the SSRU. In the SSRU, the patient-to-nurse ratio is considerably higher (i.e., nursing care in the SSRU is less labor intensive) than in the PACU. Only basic monitoring and observation are performed as the patient and his or her escort are prepared for imminent discharge to home. Because of the rapid recovery of patients undergoing anesthesia with the shorter acting, faster emergence anesthetics, some have questioned if all ambulatory surgical patients need to receive intensive postoperative care in the PACU setting or whether "first stage" recovery from anesthesia can be achieved safely while still in the operating room (at least for some patients), thereby resulting in substantial institutional savings.

The "SAFE" study evaluates the impact of selective patient bypass of the PACU on both the outcomes of ambulatory surgical patients and the use of resources in the surgical arena.[4] This study was designed to evaluate the rapid recovery of patients undergoing ambulatory surgery using short-acting, fast emergence anesthetic agents and to determine if policies and procedures could be developed that would allow patients to safely bypass first stage post-anesthesia care units (PACU) and whether such changes in the recovery paradigm would result in financial savings for the surgical center. Five community based facilities (hospitals or surgery centers) participated in this prospective observational study. While in the operating room at the end of the surgical procedure, anesthesiologists were asked to assess all ambulatory surgical patients for recovery using standardizing discharge criteria typically used at the end of a PACU stay (Table 1). If the patient met the discharge criteria, they were transferred from the OR directly to the less labor intensive second stage recovery unit (SSRU). Financial data were provided from all

five sites detailing all costs associated with the recovery process. Clinical data on every elective ASA 1, 2 and 3 ambulatory surgical patient were collected over a three month period. During month one, data collected established a baseline of case mix, time stamps, adverse events, bypass rates, and financial profile. During month two, an educational intervention was provided on a multi-disciplinary basis to all units in the surgical center discussing the implications of the fast track paradigm. After implementation of the fast track paradigm (month three) weekly feedback reports were provided to the site featuring the key outcomes of the study, and these reports were distributed to the health care providers. Nearly 5,000 patients were entered into the study. The overall bypass rate increased from 15.9% in the baseline month to 58.9% in the month following the educational intervention ($p < 0.0001$). The change in process in this study went beyond reducing time spent in the PACU to eliminating the time spent in the PACU while not increasing the time spent in the operating room or SSRU. In fact, the average (SD) time spent in the SSRU was significantly shorter for patients who bypassed the PACU than for those who did not bypass the PACU. There were no significant differences in other parameters of patient outcome. Annualized savings ranged from $50,000 to $160,000 per site.

The Hows And Whys Of Preoperative Evaluation

The continued growth of outpatient surgery has created new roles for the anesthesiologist that seemingly demand skills in addition to "giving a good anesthetic." The times from induction to emergence are no longer the only or even most important role for the perioperative physician. Particularly in the freestanding and office environments, it is often the anesthesiologist who is most involved in the direct medical care of the patient; we are the physicians who must insure that the patient is appropriately screened, evaluated, and informed prior to the day of surgery. Indeed, the anesthesiologist/patient relationship that sometimes develops often takes on a primary care quality. Although difficult to arrange, the preoperative interview and evaluation by a consultant anesthesiologist (particularly in high risk patients) can be extraordinarily beneficial. In addition to lessening anxiety about the surgery and anesthesia, in most cases, the anesthesiologist will be able to identify potential medical problems in advance, determine their etiology, and if indicated, initiate appropriate corrective measures. Additionally, the ambulatory anesthesiologist can play a critically important role in assuring that the patient understands and complies with preoperative instructions. In most facilities, the goal is to resolve preoperative problems well in advance of the day of surgery, thereby minimizing the numbers of both cancellations and complications.

The Inappropriate Patient - Who's OK And Who's Not

There are few data to reliably categorize the inappropriate adult surgical outpatient. As anesthesiologists have become more experienced with the anesthetic management of the problem surgical outpatient, the list of "inappropriate" patients has dwindled. We must individualize our decision with regard to each patient; with few exceptions, the appropriateness of a case for outpatient surgery is determined by a combination of factors including patient considerations, surgical procedure, anesthetic technique, facility capabilities, and anesthesiologist's comfort level.

At the University of Chicago Medical Center, we have distinguished several groups of patients who may not be appropriate candidates for ambulatory surgery. As one might expect, this list is frequently modified to adapt to the ever-changing conditions of our social and medicolegal environment.

• Unstable ASA Physical Status 3 and 4: At the present time we are reluctant to proceed with elective ambulatory surgery in a medically unstable patient. Instead, we use our anesthesia perioperative medicine clinic (APMC) to screen these patients, and together with the primary care surgeon or interventionalist, establish a plan to proceed with the surgery or intervention after medical stabilization. Contrary to the original "ground rules" of ambulatory surgery, studies involving hundreds of thousands of patients seem to suggest that neither increasing age nor the presence of chronic, stable pre-existing disease affect the incidence of postoperative complications in the surgical outpatient.

• Malignant Hyperpyrexia: In our facility, overnight hospitalization and observation is usually indicated for patients with a history of malignant hyperpyrexia or with identified susceptibility to malignant hyperpyrexia. However, patients who are well educated, have a good understanding of their disease process, and have ready access to medical care may be treated as outpatients by some centers.

• Complex Morbid Obesity/Complex Sleep Apnea: Although patients who have a history of sleep apnea or who are morbidly obese without systemic disease are acceptable candidates for ambulatory surgery, we prefer overnight hospitalization and postoperative observation for morbidly obese surgical patients with significant pre-existing cardiac, pulmonary, hepatic or renal compromise or those patients with a history of complex sleep apnea. Practice guidelines for the perioperative management of patients with obstructive sleep apnea have recently been updated by the American Society of Anesthesiologists and offer recommendations for preoperative evaluation, preoperative preparation, intraoperative management, postoperative management, and "site" of surgery (inpatient vs. outpatient).[6]

• Acute Substance Abuse: Because of the increased likelihood of acute untoward cardiovascular responses when one administers an anesthetic to a patient who has recently abused illicit drugs, we preoperatively counsel these patients and inform them that any sign of recent drug abuse on the day of surgery will result in immediate cancellation of their anesthetic. We tell them that no elective surgical procedure "is worth dying for" and encourage their preoperative participation in a rehabilitation program.

Anesthesiology directed perioperative medicine clinics are increasingly used to optimize the medical condition of a patient in preparation for surgery. These clinics have been shown to enhance patient safety, improve patient satisfaction[7,8], minimize preoperative consultation[9], and reduce day of surgery case cancellations and case postponements.[10] In summary, it is clear that geriatric and higher risk (physical status 3 and 4) patients may be considered acceptable candidates for outpatient surgery **if** their systemic diseases are well controlled and the patient's medical condition is optimized preoperatively.

Incomplete Reversal of neuromuscular blockade and the use of sugammadex

Incomplete reversal of neuromuscular blockade (NMB) is a common and significant problem after ambulatory surgery with a reported incidence of greater than 20% of all patients. [11,12] Morbidities typically cited as minor following inpatient surgery can lead to substantive problems delaying satisfactory recovery from a short outpatient procedure. These include but are not limited to diplopia, severe nausea, generalized weakness, difficulties with balance. Some of these morbidities can be attributed to incomplete reversal while others are often associated with anticholinesterase pharmacologic antagonism.

Sugammadex is a new (to the US) reversal agent indicated in adults for the reversal of NMB by steroidal neuromuscular blocking agents (e.g., vecuronium and rocuronium).[13] It has a unique mechanism of action. After distributing itself through the plasma it directly binds with and thereby inactivates the steroidal NMB agents and creating a concentration gradient with the NM junction. As a result, there is a shift of NMB into the plasma where it is further bound by sugammadex, thereby reducing the amount of NMB available to bind with the nicotinic cholinergic receptors at the NM junction.[14] Sugammadex does not affect the release or breakdown of acetylcholine. During the presentation, we will review the advantages and disadvantages of utilizing sugammadex for NMB reversal.

Does Choice of Anesthetic Affect the Rate of Cancer Recurrence?

There is a growing body of literature that suggests that surgery and choice of anesthetic/analgesic may have an influence on the recurrence rate of malignant tumors.[15-22] Tumor manipulation and excision leads to the dissemination of tumor cells into the vascular circulation. Surgical stress and the inflammatory response to surgery leads to a significant depression of cell mediated immunity. Multiple recent studies suggest that intraoperative and postoperative opioids may influence the recurrence and/or metastasis of malignant tumors.[23-27]

Is NAPS making a comeback? (Nurse Administered Propofol Sedation)

When propofol was originally released in 1989, it was accompanied by a US FDA "black box" warning limiting its use to practitioners trained in the administration of general anesthesia. In the late 1990's and early 2000's, RN administered propofol sedation was not infrequently utilized to facilitate interventional medicine procedures requiring patient sedation.[28,29] In 2005, the American College of Gastroenterology petitioned the FDA to again evaluate the need for this black box warning. After several years of scrutiny and consideration, in 2010, the FDA re-affirmed the "black box" warning. Of note: In 2008, the Iowa Board of Nursing announced regulatory changes in the state which permitted registered nurses to administer propofol for sedation under specified circumstances. A group from the Department of Anesthesia at the University of Iowa has recently reported on a program at their institution in which anesthesiologists or nurse anesthetists supervised RN administered propofol for sedation.[30] During this Refresher Course, we will review the safety and cost considerations as described in this manuscript.

Computer-Assisted Personalized Sedation (CAPS): Dead or Alive?

Ethicon Endo-Surgery, Inc. has developed a computer-assisted personalized sedation system (trade name SEDASYS®). According to the manufacturer, this device is the first computer-assisted personalized sedation (CAPS) system designed for physician/nurse teams to provide minimal-to-moderate sedation levels with propofol. By integrating drug delivery and patient monitoring, this computer-assisted personalized sedation device enables physician/nurse teams to deliver individualized, personalized sedation. [31] It automatically detects and responds to signs of over-sedation (oxygen desaturation and low respiratory rate/apnea) by stopping or reducing delivery of propofol, increasing oxygen delivery and automatically instructing patients to take a deep breath."

The process of getting this device to market was long and tedious. On May 28, 2009, the Anesthesia and Respiratory Therapy Devices Advisory Committee of the US Food and Drug Administration (FDA) concluded its deliberations and recommended to the FDA that the device be approvable for the administration of propofol by physician/nurse teams for the initiation and maintenance of minimal to moderate sedation during screening and diagnostic procedures in patients undergoing colonoscopy and esophagoduodenoscopy procedures, but only under the following conditions:

1) The device may only be used in adult patients (ASA I, II, and III) 70 years old or younger;
2) The device may only be used in the presence of a 3 person clinical team where one person shall have the sole responsibility of monitoring the patient, the device and managing the patient's airway. This dedicated person must have advanced training and at least the skills of a nurse;
3) Physicians utilizing the device must complete training in advanced airway management, pharmacology of propofol and opioids, patient selection, monitor training (such as SpO_2 monitoring), device set-up and maintenance with the training provided by a clinician with credentials to provide deep sedation to general anesthesia. In addition, the FDA has mandated that there be a program established for ongoing maintenance of training;
4) The manufacturer must complete all post-marketing studies as proposed at the time of the Advisory Panel hearing.
5) The product launch is "controlled."

The Anesthesia and Respiratory Therapy Devices Advisory Committee of the US FDA (composed primarily of anesthesiologists) recommended approval of the device in large part because of the demonstrated improvement in patient safety the implementation of the device appeared to provide compared to the "typical" method of moderate sedation provided by gastroenterologists (i.e., benzodiazepine/opioid parenteral titration). Nevertheless, In April 2010, Johnson & Johnson, the parent company of Ethicon-Endo Surgery, Inc., announced that the FDA sent the company a "not approvable" letter for the SEDASYS® Computer Assisted Personalized Sedation System. The company appealed this decision and on May 10, 2013 the company announced that the FDA had granted approval for launch of the device. Implementation of the launch occurred in October, 2014. Acceptance and utilization by

gastroenterologists was much slower than expected and in March, 2016, Ethicon Endo-Surgery, Inc. announced it was exiting the marketplace, thereby putting an end to the utilization of this first generation device.

It would be foolhardy to believe that such computer assisted personalized sedation devices are "dead". Traditionally, anesthesiologists have embraced technological advances in patient safety and CAPS devices will likely soon be back. Indeed, several such second generation devices are currently under development. During the session, we will review many of the specifics of the first generation of these devices and strategies for its potential incorporation into a sedation plan.

Summary

Today there is a continued trend to expand the indications for ambulatory surgery. Because outpatient anesthesia is a break from our traditional training, we are constantly being confronted with the need for change in our clinical practice patterns. We have recognized that the needs of the surgical outpatient may be very different from the inpatient and are now trying to adapt our practice patterns to meet the psychologic and pharmacologic requirements of the compacted perioperative management the outpatient receives. This Refresher Course has focused on some of the controversial problems that we as practicing clinicians must deal with every day in our practice of ambulatory anesthesia for adult patients.

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TABLE 1. DISCHARGE CRITERIA

- Awake, alert, oriented, responsive (or return to baseline)
- Minimal pain
- No active bleeding
- Vital signs stable (not likely to require pharmacologic intervention)
- Minimal nausea
- No vomiting
- If nondepolarizing neuromuscular blocking agent used, patient can perform sustained five second head lift
- Oxygen saturation of 94% on room air (three minutes or longer) OR return of oxygen saturation to baseline or higher in order to be eligible to bypass Phase I recovery (PACU), the patient must meet ALL of the above criteria, and in the judgment of the anesthesiologist, be capable of transfer to the step-down unit, with appropriate care and facility for patient management at that location

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Assessment of Competence: Developing Trends and Ethical Considerations

Melissa Chin MD, FRCPC — **London, Ontario, Canada**
Robert Lagasse, MD — **New Haven, CT**

Introduction

The assessment of clinical competence is a topic of growing global interest, particularly as competency-based medical education becomes a reality in the United States and Canada, as well as other parts of the world. There are many reasons for this, not least of which is the landmark report *To Err is Human* by the Institute of Medicine in 1999. This report placed the public spotlight on medical error, likening the incidence of medical error leading to death as the equivalent of a Boeing 747 crash every two days.[1] Since then, there has been a paradigm shift in the way that patients and health professionals think about education, with an increasing demand for accountability and a decreased tolerance for medical error.

Our traditional assumption is that competence is achieved with increasing years of exposure. But, with competency-based training, it is important to consider time and expertise as two separate entities. Time thus becomes a resource to be used to achieve expertise, rather than a marker of expertise in and of itself. [2] In order to separate the judgment of competence from length of training, the identification and assessment of explicit competencies by reliable and valid tests is required.[3]

Current Assessment Methods

Broadly, there are two different types of assessments. Formative assessments are those that are used for education and training; these are generally considered as feedback for continuous improvement. Summative assessments are those that are used to formulate decisions about a candidate. With regards to decisions of competence, the goal is generally to decide whether the candidate can be board-certified, or in some cases, can return to work as a practicing anesthesiologist after a prolonged leave of absence. Similar to other scientific tests, there are two important aspects of a summative assessment that must be evaluated prior to its application: validity and reliability. Validity refers to the test's ability to measure what it is designed to measure. Reliability refers to the reproducibility of the test.

Traditional assessment methods used today include familiar forms such as written tests, structured oral examinations, direct observation, simulation-based assessments and objective structured clinical examinations (OSCEs). The rigor and the frequency of these assessments are not standardized and can vary from training program to training program. Further, when compared to the stages of attainment of competency on Miller's pyramid, most of these assessments are fairly removed from assessing what an anesthesiologist does or is required to do on a daily basis as part of providing patient care.[4]

Competencies can be broadly categorized as technical or non-technical skills. Technical skills refer to the knowledge and procedural expertise required for practice. Non-technical skills refer to the cognitive and behavioral expertise required for practice, such as communication, interpersonal skills, and decision-making.

Assessment of Technical Skills

Technical skills are fairly well assessed using traditional methods of assessment, most notably through the use of procedural checklists. Current research now focuses on the design and validation of these checklists in order to show that they can be used in competency-based education. For example, Woodworth et al. and Chuan et al. were among the first to design and validate checklists for use in testing ultrasound image interpretation and regional anesthesia procedural skills, respectively.[5,6] Other researchers have focused on incorporating psychology into the development of checklists by such methods as hierarchical task analysis, for example. Breen et al. have done this in the development of a competency checklist for spinal anesthesia.[7]

These methods for assessing technical skills are nevertheless labor-intensive in their development. As such, some others have studied whether available data sources, such as electronic medical records, are capable of providing markers of competence. Inoue et al. performed a study to determine whether any relationship between the incidence of postoperative throat complications and level of training. They however did not find any correlation.[8] Another group led by Sessler et al. attempted to determine whether there was any relationship between duration of intraoperative hypotension and external evaluations of trainees by faculty and in-training exam performance. Again, there was no correlation. [9]It is possible that there is data contained within electronic medical records that can be used to evaluate clinical competence, however, what that data is remains to be elucidated.

Assessment of Non-Technical Skills

Non-technical skills are typically less easily evaluated with traditional assessments. This led to the development of the Anaesthetists' Non-Technical Skills behavioral marker system. This system evaluates observable, non-technical behaviors that have been previously shown to contribute to superior or substandard performance. [10]In other words, it provides a tool for assessing aspects of performance that were previously judged subjectively by 'gut feelings.' The ANTS system was developed a number of years ago, and more recently, there have been studies evaluating it in different countries showing its validity across different cultures and styles of practice. [11,12]

Another aspect of non-technical skills that has recently received a lot of attention is specifically that of clinical reasoning ability. New research has shown the validity of using a "Script Concordance Test" to distinguish level of training. This paper-based evaluation tool compares how examinees make clinical decisions based on vignettes of information with expert responses, and has been shown to distinguish between junior, senior, and expert level groups.[13]

Simulation-Based Assessment

Simulation has recently been highlighted as a method to perform high-stakes summative assessments for a number of reasons. Since it has the capacity to present multiple different clinical events, it is possible to evaluate multiple technical and non-technical skills at once. Chiu et al. describe the use of such assessments in the creation of the CanNASC program, a summative assessment program being developed in Canada for all senior level trainees.[4] In addition, because simulation scenarios are created, it is possible to standardize each encounter for all examinees, which would not be possible otherwise in direct observation of daily clinical practice. Another commonly cited advantage of simulation is the ability to debrief candidates after their performance. This allows examiners to elicit information regarding the motivation and clinical reasoning behind actions exhibited in a simulation session. Sidi et al. performed a fascinating study examining the incidence of cognitive errors (anchoring bias, availability bias, confirmation bias etc.) through debriefing, and found a higher incidence of these types of errors than technical errors or knowledge deficits. [14]

Challenges in Designing and Implementing New Assessment Methods

There are a number of ethical, and potentially legal challenges in the use of competency-based assessments for high-stakes decisions that must be addressed before its widespread use. Firstly, there has been significant discussion regarding the definition of competence itself. At first glance, clinical competence is a subject that is thought of as being universally understood. Yet, when broken down into its many parts, there remains an element of subjectivity to it that cannot seem to be eliminated. A working definition for competency-based medical education has been suggested[15], but the path to reaching competence is still not universally defined.

Secondly, there is new research within the educational field that now challenges the idea of a test being validated once in an experimental setting and subsequently being applied to many different settings. Some now argue that validity should be considered a process or an argument rather than a quality of the test. [16] This approach places more of an emphasis on the decisions that are to be made based on the results of the test in question. As the stakes of assessment become higher – the determination of competence or incompetence for board certification, the decision to return to work after a leave of absence due to any number of reasons – the level of evidence required

becomes higher. And yet, we must also confront the reality that it is extremely unlikely that there will be a perfect test for clinical competence. As with any scientific test, there will likely be a percentage of associated alpha and beta error, and as such, a certain number of physicians who will be incorrectly judged as competent or incompetent. This raises ethical and legal concerns in withholding certification from physicians who are competent, and in exposing patients to certified physicians who may be incompetent.

Thirdly, as we have seen with the assessment methods described above, there is a significant investment of time, resources, and finances required for their implementation. While there is great promise in the use of simulation for summative assessments in terms of its validity and reliability, it is also associated with substantial cost. If objective measures of competence are to become the standard in medical education and licensure, it will be necessary to find ways to decrease the financial burden and resources required. [17]

Conclusion

The paradigm shift in the public eye and within the medical community itself has motivated the search for objective and valid measures of competence in anesthesia. As new methods of assessing competence are devised, reliability and validity testing become increasingly important due to the nature of the decisions that will be made based on these tests. Current methods require significant investment of resources and a more financially feasible, yet equally valid and reliable, method is needed to meet the demands of competency-based medical education, maintenance of certification, and licensure.

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Regional Anesthesia Registries: Is There Value and What Have We Learned

Michael Barrington Ph.D. **Melbourne, Victoria, Australia**

Regional Anesthesia Registries: Is There Value and What Have We Learned?

Introduction

Clinical registries provide a snap shot into how healthcare performs.[1] The focus of clinical registries is to capture real-world clinical practice, for example native hospital behaviour, in large patient populations independent of the environment of a controlled clinical trial. Clinical conditions, procedures, therapies or entire populations can be systematically studied. In the context of modern healthcare expectations where all procedures that we offer our patients should be evidenced-based, clinical registries provide a valuable tool to evaluate what works and what does not. As regulators, administrators and health funds seek more information on the quality and safety of our clinical care, registries are becoming increasingly seen as valid sources of data. During this refresher course lecture the methodology and logistics of a registry will be reviewed. Registries will be compared with other study types and will demonstrate how registries and reports with similar methodologies add value to healthcare and assist in our clinical decision-making. Ongoing monitoring of the quality and safety of regional anesthesia is important because clinical practice is continually evolving.

Methodology

Clinical Registries systematically and uniformly collect information from people who undergo a procedure, are diagnosed with a disease or use a health care resource.[2] The American Heart Association defines a clinical registry as a prospective observational database of a clinical condition, procedure, therapy or population, in which there are no registry-mandated approaches to therapy and relatively few inclusion and exclusion criteria.[3] In contrast, rigid filters in the form of inclusion and exclusion criteria are often applied before sampling can occur for a randomized controlled-clinical trial (RCT). Clinical registries serve multiple functions including monitoring and benchmarking the quality of clinical care.[4] Registries can be vehicles for public health surveillance, quality-improvement, performance assessment, evaluation of clinical trends and to monitor the safety and effectiveness of a new drug, device or procedure. Registries aim to have complete, or almost complete capture of all eligible procedures and patients, thereby minimizing selection and enrolment bias.[2] Capturing complete, or a near complete patient population with sequential enrolment is the goal. Population-based studies using existing large databases and other data sources aim to enrol an entire patient population and therefore have features similar to a registry.

The data elements that registries collect should be carefully considered and be epidemiologically sound. The data should be simple, objective and reproducible. Only data that are required to address the question or issue of interest should be collected. Appropriate data include patient demographics, surgical characteristics, anesthetic type and dosage, practice patterns, clinical effectiveness outcomes and adverse events. The data elements need not be static, but may change according to the clinical questions. Logistically the data should be simple enough so that physicians can efficiently enter information into a database in the context of a busy clinical practice. An online interface whereby data is entered to the same database and stored securely in a remote server is a valuable resource for a multicenter registry.

Methods of collecting and type of data vary depending on the outcome. For example, a registry aiming to capture peripheral nerve block (PNB)-related neurologic complications requires: 1. Systematic postoperative contact with patients using a standardized questionnaire. A systematic proactive approach to capturing complications is more likely to capture complications compared to a passive approach.[5] 2. A defined follow-up and neurologic referral and investigative pathway. 3. Clear definition for nerve injury. 4. Robust neurologic evaluation with a focused history and examination.

Registries, because they contain uncontrolled observational measurements, have a high risk for unrecognised bias and incorrect conclusions about cause and effect. This stems from the influence that unmeasured or unknown confounders may have on the results.[6] A RCT aims to randomise a sufficiently large sample to eliminate significant baseline differences between study groups and reduce bias from residual confounders. RCTs represent the gold standard for evidence of causality. The analysis of observational datasets may establish association but not causality,

however this type of finding may be significant when large samples are involved. The large sample size may add to the credibility of the finding. The results of observational studies are generally considered exploratory, non-definitive and generate a hypothesis to be tested in a subsequent RCT. However, this is an impractical paradigm for serious outcomes that occur so infrequently that a subsequent RCT may require a very large sample size.

What have we learned from clinical registries of regional anesthesia and other large observational population based studies and non-randomized datasets?

Registries have documented the incidence of infrequently occurring complications facilitating risk assessment and informed consent. Registries have identified that following hip and knee arthroplasty, regional anesthesia is not associated with an increased risk of perioperative nerve injury (PNI).[7,8] Fortunately, block-related neurological complications with severe long-term sequelae directly related to peripheral nerve block (PNB) or neuraxial anesthesia (NA) occur very infrequently or rarely. In one registry report, patients who met the criteria for referral to a neurologist were 9 times more likely to have a cause unrelated to PNB, than they were to have symptoms/signs attributable to PNB.[9] Without careful evaluation, patient's postoperative neurologic features can be incorrectly attributed to regional anesthesia. The potential for these scenarios are similar to obstetric practice where complications with surgical or patient etiologies can be attributed to regional anesthesia.[10] Large registries of PNB, because of their large sample size have been able to estimate the incidence of PNI.[11,12] Similarly, registries and large-scale population studies have provided contemporary estimates of complications and risk factors associated with neuraxial anesthesia.[13] Practice patterns and complications in pediatric practice have been documented systematically in registries.[14,15] The investigators of a pediatric registry concluded that performing regional anesthesia under general anesthesia does not present additional risk to the patient compared to if the patients were awake or lightly sedated.[16] These insights provide information that can be used in practice guidelines. Refer to table 1 for more detail on nerve injury.

One registry of PNB reported the incidence of pneumothorax following ultrasound-guided supraclavicular block to be 0.4 per 1000 PNB[17] and has documented reduced doses of ropivacaine when ultrasound-guided PNB was compared to non-ultrasound techniques [1.48 (0.73 – 2.71) versus 1.63 (0.74 – 2.88) mg/kg respectively, doses presented as median (10^{th} – 90^{th} centile)].[18] Reduced local anesthetic dosage may reduce the risk of local neural and systemic toxicity and reduce the incidence of side effects such a phrenic nerve paralysis following interscalene blockade.

Fortunately, registries indicate that severe local anesthetic systemic toxicity (LAST) occurs infrequently or rarely.[19] One single-center study recorded an incidence of seizures of 0.92 per 1000 PNB in a practice where landmark, nerve stimulator and ultrasound-guided techniques were used.[20] All of seizures occurred in patients where either landmark or nerve stimulator techniques were used. In a follow-up study at the same institution, one further seizure occurred, again in a patient receiving a non-ultrasound technique.[11] In a multicenter registry of 8189 PNB there were five and four episodes of minor and severe LAST respectively. The overall incidence of LAST was 0.98 per PNB with no significant difference between ultrasound-guided and non-ultrasound techniques.[9] In 2012, using a single-centre registry there were no cases of severe LAST (seizures) reported from a cohort of 12,668 ultrasound-guided PNB.[12] In 2013, data (25,336 PNBs from 20,021 patients) was analyzed from the Australian and New Zealand Registry of Regional Anaesthesia. The results demonstrated that ultrasound-guidance was significantly associated with a reduced risk of LAST.[18] The risk of LAST was reduced by 60 – 65% when ultrasound was used compared to use of nerve stimulation or landmark techniques for PNB. In this report, the overall incidence of LAST was 0.87 per 1000 PNB. Importantly, this study also identified factors associated with an increased risk of LAST including site of injection (upper limb blockade, paravertebral), local anesthetic dosage, local anesthetic dosage per weight, and reduced patient body weight. Independent of factors related to ultrasound and those identified in the abovementioned studies, it is generally accepted that patient comorbidities and individual susceptibility to local anesthetic may increase the risk of LAST. Overall the risk of LAST, calculated from registries and similar studies is approximately 0.36 per 1000 PNB. Refer to table 2 for more details on LAST.

Patient rated outcomes can be included in a registry to reflect the importance of patient centred care. In one registry report, 94.6% of respondents were willing to have a repeat PNB. Ninety percent of respondents were satisfied or completely satisfied with the information provided about the nerve block, as well as the anesthesiologist-patient interaction. Patients who were dissatisfied with either of these domains (ie, information provision or professional interaction) were less willing to undergo repeat PNB, as were patients who reported significant pain during the nerve block procedure. These findings have practical implications for conduct of PNB.[21]

Recently the presenter was fortunate to be part of research team that performed a meta-analysis of observational studies and non-randomized datasets comparing general with neuraxial anesthesia, with primary outcome being mortality (table 3).[22] This analysis included 6 studies,[23-28] and resulted in no reduction of odds of 30-day mortality (OR 0.88; 99% CI 0.77 to 1.01). Analysis of observational studies comparing neuraxial anesthesia versus general anesthesia alone, included 13 studies,[23,24,27,29-38].and there was no reduction in the odds of 30-day mortality (OR 0.98, 99% CI 0.92 to 1.04). When combined neuraxial-general anesthesia was compared with general anesthesia, combined neuraxial-general anesthesia was associated with a reduced odds of pulmonary complication (OR 0.84; 99% CI 0.79 to 0.88), surgical site infection (OR 0.93; 99% CI 0.88 to 0.98), blood transfusion (OR 0.90; 99% CI 0.87 to 0.93), thromboembolic events (OR 0.84; 99% CI 0.73 to 0.98), length of stay (Mean difference -0.16 days; 99% CI -0.17 to -0.15), and ICU admission (OR 0.77; 99% CI 0.73 to 0.81). There was an increased odds of myocardial infarction (OR 1.18; 99% CI 1.01 to 1.37). A plausible mechanism for this increase in myocardial infarction for patients receiving combined neuraxial-general compared to general anesthesia alone may be the potential for sympathetic block and resultant hypotension associated with the combined anesthetic technique, however due to the observational nature of the dataset, no causal mechanism for this result can be established. There was no difference in the odds of pneumonia (OR 0.94; 99%CI 0.87 to 1.02) or cardiac complications (OR 1.04; 99% CI 1.00 to 1.09).

Registries provide value

Clinical registries and the actions of our professional groups add value to healthcare reporting by: 1. Developing epidemiological tools to enhance the knowledge base about quality and safety; 2. Establishing voluntary reporting tools to identify and learn from errors; 3. Raising the standards and expectations in patient safety; 4. Contribute to building and maintaining a culture of safety; 5. Providing an opportunity for local leadership and 6. Proactively monitor for adverse events. Registries add value by providing the infrastructure to support ongoing data collection and providing insights into long-term efficacy and safety that a single trial may not be able to detect. Time series data can validate earlier findings and detect trends in practice. Patterns in time series data contain important information that other traditional statistical methods reliant on averages or summary statistics can mask. Improvement is a temporal event and incorrect claims of improvement or efficacy become apparent with time.[6] The science and practice of medicine move quickly and the original clinical environment of a trial may no longer exist by the time its results are being applied. A registry, because of its longevity, is more flexible in terms of identifying trends in practice and results relevant to contemporary care.

Conclusions

Registries and related population-based studies including a variety of surgical cohorts have provided essential insights into the quality of healthcare, providing opportunities to report and improve outcomes that both physicians and patients consider important. The incidence of major morbidity related to PNB or neuraxial anaesthesia is fortunately uncommon or rare. Neuraxial anesthesia when used alone or when combined with general anesthesia may improve important perioperative outcomes when compared with general anesthesia. However, because of the risk of residual confounding with non-randomized datasets these results should be interpreted with caution. Registries provide an important tool to report perioperative outcomes required for the modern healthcare paradigm. Registries of regional anesthesia are instrumental for defining the quality and safety of clinical practice.

Table 1. Nerve injury: summary of results from selected registries and population-based studies.

Author, Year	Anesthesia type	N, cohort	Outcomes	Main results
Barrington, 2009[9]	PNB	8189 PNB	Neurological complication, LAST	Nerve injury, 0.4 per 1000; LAST, 0.98 per 1000 PNB
Liu, 2010[39]	Interscalene/ supraclavicular blocks	1169	Nerve injury	0% incidence of permanent nerve injury
Jacob, 2011[8]	PNB	12,329 TKA	Nerve injury	Nerve injury not associated with PNB or anesthesia type
Jacob, 2011[7]	PNB	12,998 THA	Nerve injury	Nerve injury not associated with PNB or anesthesia type

Orebaugh, 2012[11]	PNB	9069 US guided 5436 NS guided	Nerve Injury Seizure	US and NS blocks: No difference in nerve injury rate, increased seizures with NS blocks
Sites, 2012[12]	PNB	12,668 PNBs	Nerve injury, LAST Pneumothorax Vascular trauma	Event rate:1.8 per 1000, major complications occurred rarely
Polaner, 2012[15]	All RA types	14,917 PNB	Practice patterns and complications in pediatric practice	No complications >3 months. 95% of PNB were placed under GA PNBs used in 35%
Sviggum, 2012[40]	Interscalene	1569 TSA	Nerve Injury	PNB associated with reduced risk for nerve injury
Barrington, 2013[18]	PNB	25,336 PNB	LAST	LAST, 0.87 per 1000 PNBs. Ultrasound guidance was associated with reduced incidence of LAST.
Sites, 2014[41]	PNB	23,271 PNB	Safety and effectiveness	Immediate complication, 2.2% All cause 60-day neurological sequelae, 0.83%,
Taenzer, 2014[16]	PNB	53,564	Nerve injury/symptoms	Neurological symptoms :0.93/1000 (0.7–1.2) under GA; 6.82/1000 (4.2–10.5), in sedated/awake patients, (95% CI)
Long, 2014[14]	TAP blocks	1994	Morbidity	Complications: 0.1% (0.02%–0.3%, 95% CI)

Table 2. LAST: summary of results from clinical registries, observational and administrative datasets.

Author, Year	LAST events, n	N	Incidence of LAST following PNB		Regional Anesthesia	Setting	Presenting features
			n per 1000	%			
Ecoffey, 2010[42]	3	18, 375	0.16	0.02	Neuraxial[1]: 10,556 Peripheral: 18,735	Pediatric	Major LAST
Orebaugh, 2012[11]	6	14,498	0.41	0.04	Peripheral	Single-center academic	Major LAST
Sites, 2012[12]	0	12,668	-		Peripheral	Single-center academic	Events sought were seizures
Polaner, 2012[15]	0	14,917	0 – 2[#]		Neuraxial[2]: 9,156 Peripheral: 5,761	Pediatric, 6 academic centers	
Barrington, 2013[18]	22	25,336	0.87	0.09	Peripheral	Multi-center, academic,	Minor LAST, 13;

						community hospitals	major LAST, 8, cardiac arrest, 1
Rohrbaugh, 2013[43]	8	15,014	0.53	0.05	Interscalene		Details not provided
Gurnaney, 2014[44]	3	1,954	1.53	0.2	Peripheral	Pediatric, Single-center academic	Outpatient catheters, minor LAST
Heinonen, 2015[45]	14	38, 350	0.37	0.04	Peripheral[3]:38,350 neuraxial[4]	Nationwide study	Major LAST
Liu, 2016[46]	3	80,661	0.04	0.004	Peripheral	Single-center, high-volume practice	Major LAST
Allegri, 2016[47]	10	29, 545	0.34	0.03	Peripheral: 29,545 Neuraxial: 34,147	Multi-center	Minor LAST, 3 ; major LAST, 7
Morwald, 2017[48]	434	238,473	1.8	0.18	Peripheral	Administrative database	Surrogate markers for LAST

n = number of events following peripheral nerve blocks (PNB),; N = denominator of PNB; Total number of LAST events and denominator from clinical registries is 69 and 251,318 respectively giving an incidence of 0.03% or 0.27 per 1000 PNB; [#]95% confidence interval per 10,000 presented for zero events, calculated by author; GA, general anaesthesia; [#]1 event presented as unconsciousness followed by seizure; 1. Included 387 episodes of spinal anesthesia, incidence of LAST following neuraxial blockade was 1.2 per 1000; 2 Included 83 episodes of spinal anesthesia; 3. Refers to perioperative peripheral nerve blockade; 4. Spinal anesthesia excluded from denominator of 211,700. ILE, intravenous lipid emulsion.

Table 3. Perioperative outcomes: summary of results adapted from Smith et. al.[22]

Outcomes	**Anticipated absolute effects*** (99% CI)		**Relative effect (99% CI)**	**Number of participants (studies)**
	General Anesthesia	**Neuraxial Anesthesia**		
30- day Mortality GA, GA+NA	6 per 1,000	**6 per 1,000** (5 to 6)	**OR 0.88** (0.77 to 1.01)	396869 (6 observational studies)
30- day Mortality GA, NA	10 per 1,000	**10 per 1,000** (9 to 11)	**OR 0.98** (0.92 to 1.04)	491611 (13 observational studies)
Myocardial Infarction GA, GA+NA	5 per 1,000	**6 per 1,000** (5 to 7)	**OR 1.18** (1.01 to 1.37)	471812 (4 observational studies)
Myocardial Infarction GA, NA	5 per 1,000	**4 per 1,000** (4 to 5)	**OR 0.91** (0.81 to 1.02)	520052 (9 observational studies)

Cardiac Composite GA, GA+NA	75 per 1,000	**78 per 1,000** (75 to 81)	**OR 1.04** (1.00 to 1.09)	361143 (2 observational studies)
Cardiac Composite GA, NA	60 per 1,000	**60 per 1,000** (57 to 62)	**OR 0.99** (0.94 to 1.03)	447748 (11 observational studies)
Pulmonary Composite incl. ventilation GA, GA+NA	67 per 1,000	**57 per 1,000** (54 to 60)	**OR 0.84** (0.79 to 0.88)	459433 (3 observational studies)
Pulmonary Composite incl. ventilation GA, NA	35 per 1,000	**14 per 1,000** (13 to 14)	**OR 0.38** (0.36 to 0.40)	498229 (9 observational studies)
Pneumonia GA, GA+NA	28 per 1,000	**27 per 1,000** (25 to 29)	**OR 0.94** (0.87 to 1.02)	471812 (4 observational studies)
Pneumonia GA, NA	13 per 1,000	**12 per 1,000** (11 to 13)	**OR 0.92 (0.84 to 1.01)**	396106 (8 observational studies)
Surgical Site Infection GA, GA+NA	53 per 1,000	**49 per 1,000** (47 to 52)	**OR 0.93** (0.88 to 0.98)	459433 (3 observational studies)
Surgical Site Infection GA, NA	42 per 1,000	**32 per 1,000** (30 to 34)	**OR 0.76** (0.71 to 0.82)	380682 (7 observational studies)
Blood Transfusion GA, GA+NA	177 per 1,000	**162 per 1,000** (158 to 167)	**OR 0.90** (0.87 to 0.93)	459433 (3 observational studies)
Blood Transfusion GA, NA	189 per 1,000	**166 per 1,000** (161 to 171)	**OR 0.85** (0.82 to 0.88)	369653 (6 observational studies)
Blood Transfusion GA, NA (RCTs)	155 per 1,000	**163 per 1,000** (101 to265)	**RR 1.05** (0.65 to 1.71)	585 (5 RCTs)
Thromboembolic complications GA, GA+NA	9 per 1,000	**8 per 1,000** (7 to 9)	**OR 0.84** (0.73 to 0.98)	459433 (3 observational studies)
Thromboembolic complications GA, NA	6 per 1,000	**4 per 1,000** (4 to 5)	**OR 0.79** (0.68 to 0.91)	397806 (7 observational studies)

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Antifibrinolytics: What is the Safety Profile of Tranexamic Acid in Cardiac Surgery?

C. David Mazer MD FRCPC **St. Michael's Hospital, Univ of Toronto, Toronto, ON Canada**

Antifibrinolytic drugs are commonly used to minimize bleeding during cardiac and non-cardiac surgery and are considered the standard of care for some procedures. Tranexamic acid (TXA) is a lysine analogue antifibrinolytic agent which acts by reversibly binding to plasminogen and thereby competitively inhibiting the binding of the fibrin-degrading enzyme, plasmin to fibrin.[1] Reduced fibrinolysis leads to the stabilization of the fibrin clot and can reduce perioperative bleeding by up to 30%. The initial FDA approval for TXA was for patients with hemophilia undergoing dental surgery and women with heavy menstrual bleeding, but beneficial blood-sparing effects have been reported in wide variety of clinical settings including cardiac surgery, orthopedic surgery, gastrointestinal bleeding, trauma and intracerebral and postpartum hemorrhage.
The STS/SCA Blood Conservation Guidelines has a Class I Level of Evidence A recommendation for the use of lysine analogues—epsilon-aminocaproic acid (EACA, Amicar) or tranexamic acid (Cyklokapron) to reduce total blood loss and decrease transfusion in cardiac surgical procedures[2]. TXA was recently included on the World Health Organization's 'Model List of Essential Medicines' which recommends the use of TXA in trauma, postpartum hemorrhage and cardiac surgery with cardiopulmonary bypass.

Tranexamic acid ($C_8H_{15}NO_2$) is an isomer of 4 aminomethylcyclohexane carboxylic acid which competitively inhibits plasminogen by binding to both strong and weak lysine binding sites on plasminogen.[1] Lysine analogues inhibit both clot-bound and free plasmin. TXA is a weak acid (pKa ~4.3), is non-lipophilic and has poor affinity for other plasma proteins. TXA obeys first-order kinetics best described with a two-compartment model.[3,4] Up to 95% of TXA is excreted unchanged in the urine so total body clearance approximates the glomerular filtration rate. Pharmacokinetic properties in adults include: peripheral volume of distribution = 10.8 L, volume of central compartment = 6.6L, clearance = 4.8L/h, diffusional clearance=32.2L/hr. Drug levels may be affected body weight and renal function, so renal failure may result in higher and prolonged drug levels.[5] Lysine analogues including TXA may result in benign and reversible intaoperative proteinuria.[6]

Many studies using a variety of dosing regimens have confirmed the efficacy of TXA in terms of reduction in bleeding, transfusion and/or reoperation. For example, in a recent large RCT, Myles et al reported that TXA significantly decreased transfusion of any blood products, need for reoperation, length of mechanical ventilation and length of ICU stay with no increase in adverse thrombotic outcomes compared to placebo.[7] Nonetheless, the optimal dosing regimen for TXA in cardiac surgery remains to be determined. The BART dose was developed to target serum TXA concentrations of ~ 800 umol/L, although the actual levels achieved with this dose are variable and often higher.[3,5,8-10] For tissue activators for fibrinolysis, TXA levels >60, 150 and 600 umol/L are thought to be required for 80 %, 90% and 98% reduction in activity respectively. In vitro reports have suggested that concentrations of TXA as low as 30 umol/L can inhibit fibrinolysis, but levels >60 umol/ml are needed for 90% platelet activation inhibition in a plasmin pre-incubated in-vitro model.[11]

Table. TXA dosing regimens for adult cardiac surgery.

Reference study name or first author and year	*Bolus dose*	*CPB dose*	*Infusion dose*
BART (NEJM 2008, Anaesth 2012)[8]	30 mg/kg	2 mg/kg	16 mg/kg/hr
Karski (JTCVS 1995)[12]	10 g	-	2 g/hr (for 5 hours)
Grassin-Delyle (BJA 2013)[13]	46 mg/kg	-	9 - 11 mg/kg/hr
Dietrich/Karski (JTCVA 1993,A&A 2008)[14,15]	6 g	-	-
Bokesch/ BfArM (JTCVS 2012)[16]	1 g	500 mg	400 mg/hr

Fiechtner (A&A 2001)[17]	6.4 mg/kg	20 g/L	5 mg/kg/hr
Australia Product Monograph	15 mg/kg	0.6 mg/kg	4.5 mg/kg/hr
Horrow (Anesth 1995)[18]	10 - 40 mg/kg	-	1 - 4 mg/kg/hr
Abrishami (CJA 2009)[19]	1 - 2.5 g (topical)		-

CPB, cardiopulmonary bypass

Data on efficacy of different TXA dosing regimens is available from recent randomized trials. In the ATACAS study, high dose patients had less bleeding and fewer units of blood transfused (100mg/kg vs 50 mg/kg total dose).[7] Sigaut et al randomized patients to receive either 10 mg/kg bolus followed by 1 mg/kg/hr infusion (low dose) or 30 mg/kg bolus followed by 16 mg/kg/hr infusion (high dose).[20] The high dose group had lower blood loss, less repeat surgery and lower incidence and amounts of transfusion of blood products including platelets and plasma. Similarly, Bokesch et al reported results from 2 different TXA doses (30 mg/kg load, 16 mg/kg/hr infusion during surgery, and 500 mg in pump prime (similar to BART dose) compared to a low dose group who received 1000-mg loading dose 400 mg/hr infusion, 500 mg added to the pump prime.[16] In that study, TXA had a significant dose effect with less bleeding and higher volumes of PRBCs transfused to the 85 patients who received the lower, dose of TXA compared with the 24 patients who received twice the labeled dose of TXA. Furthermore, all cases of massive bleeding, re-thoracotomy, renal failure, seizures and death in the TXA group occurred in patients who received the lower dose of TXA. In 1995, Horrow et al recommended that 10 mg/kg load plus 1 mg/kg/hr was the lowest effective dose of TXA.[18] On the other hand, Faraoni et al found no difference between placebo or high or low dose TXA in thromboelastography measured fibrinolysis or clinical outcomes in a small study of 33 cardiac surgery patients[21], and Sharma et al reported paradoxical changes in clotting time FIBTEM and MCF in medium risk patients treated with TXA.[22] Mixed results in terms of effectiveness have been reported for the use of topical TXA in cardiac surgery.[19,23]

Several polymorphisms of coagulation and platelet genes have been found to be associated with increased bleeding after surgical procedures. For example, patients with certain genotypes of plasminogen activator inhibitor (PAI-1) are at risk of greater bleeding and thus may derive greater benefit from antifibrinolytic drugs. Current and future studies will help clarify which patients and procedures have the greatest effect. Conversely, there is theoretical concern that patients with normal coagulation or prothrombotic gene mutations such as Factor V Leiden, protein C deficiency or prothrombin gene mutations may be predisposed to thrombotic complications with the use of antifibrinolytic agents.[24,25] A recent study demonstrated that TXA increases clot resistance to fibrinolysis by several fold, but has no effect clot formation or clot stability.[26]

Seizures and Cardiac Surgery:

With increasing use of high dose TXA in cardiac surgery, there has been an increase in the reports of early postoperative seizure-like activity.[7,27-33] While the vast majority of such events have been reported in cardiac surgery, TXA associated seizures have also been reported in the setting of spine surgery, neurosurgery, renal failure and hemoptysis. The reported incidence of TXA associated seizure in cardiac surgery ranges from less <1% to >6% depending on a variety of factors including observational vs randomized trials, type of surgery and dose of TXA used. In the ATACAS randomized trial, the incidence of seizures was 0.7% in the TXA group and 0.1% in the placebo group[7], whereas an observational trial by Martin et al reported that clinically diagnosed generalized seizures occurred in up to 7.9% of patients undergoing high risk and valve procedures.[27] Risk factors for seizures after cardiac surgery include pre-existing neurologic, cardiovascular or renal disease, type of surgery, female gender, high disease severity score, deep hypothermic circulatory arrest, long CPB time, or extended aortic crossclamp time.[28-30] In general, postoperative seizures, especially those caused by stroke or structural brain injury, can be associated with adverse outcome including delirium, increased hospital stay and other morbidity and mortality. However, in the absence of structural brain injury, it is unlikely that isolated TXA associated seizures lead to adverse outcome.

The involuntary motor activity reported after TXA administration can include localized muscle twitching, focal myoclonic movements, or focal or generalized tonic-clonic seizures. These events generally occur within 6-24 hours of surgery, frequently when the effects of anesthesia and postoperative sedation are dissipating. TXA associated seizures are usually of short duration and either terminate spontaneously or with a small dose of medication. Benzodiazepines, phenytoin or other anticonvulsant drugs may be given; propofol seems especially effective. In laboratory studies, propofol and isoflurane completely reverse the hyperexcitability effects of TXA.[33,34] Dexmedetomidine may also theoretically prevent or treat TXA associated seizures, although it has not been well studied. Recurrence of seizure may occur, but does not result in status epilepticus. Nonconvulsive seizure appears to be rare in cardiac surgery patients and a prospective study concluded that prophylactic continuous EEG monitoring doesn't appear to be cost-effective in these patients.[35] However, EEG may help differentiate seizures from other involuntary motor activity. Several retrospective or observational studied report a dose effect with seizures, such that lower TXA doses are associated with a lower incidence of seizures. This is in contrast to the RCTs by Myles, Sigaut and Bokesch mentioned above in which there was no difference in seizure rate between high and low TXA doses.[7,16,20]

The mechanism for the association between tranexamic acid and seizure is likely mediated by receptor binding in the central nervous system. TXA has been shown to bind to glycine, $GABA_A$, NMDA and glutamate receptors in the brain and spinal cord.[34,36,37] Of these, glycine receptors may be the most likely mediator since the inhibitory concentration of TXA is lowest for this pathway.[34] Inhibition of such receptors can decrease inhibitory neurotransmission (or disinhibition) and generate hyperexcitability and seizure-like activity in animals. One of the puzzling questions has been why TXA-associated seizures occur in the postoperative period when serum levels would likely be declining. We measured CSF levels of TXA in a study of patients who were undergoing surgery with deep hypothermic circulatory arrest and who had a spinal drain inserted. Interestingly, we found that as expected the serum TXA levels declined rapidly when the drug infusion was stopped, whereas the CSF TXA levels continued to rise, peaking in the early postoperative period.[34] In addition, co-administration of cephalosporins and pencillin may potentiate the disinhibitory effects of TXA via $GABA_A$ receptors inhibition.

It is likely that increased permeability of the blood-brain-barrier during cardiac surgery may contribute to the pathophysiology of seizures following TXA administration, although the mechanism for this is unknown. It has been suggested that increased systemic inflammatory cytokines during cardiac surgery may increase blood-brain-barrier permeability, enabling for TXA to enter the central nervous system.[38] Also changes in tissue plasminogen activator (tPA) may induce modulation of blood-brain-barrier (BBB) permeability. tPA is highly expressed in the central nervous system. Cardiac surgical procedures with CPB have been associated with elevated concentrations of plasma tPA levels.and experimental models have demonstrated that increases in tPA are associated with increases in permeability of the BBB via platelet growth factor binding with receptors and lipoprotein complexes.[39-41] In addition, TXA associated seizures appear to occur more frequently in patients undergoing non-CABG open-chamber procedures or after DHCA in which the BBB permeability may be increased from other metabolic or embolic causes.

Amicar (EACA), which is structurally similar to both TXA and glycine, also competitively inhibits glycine receptors with a 10 fold lower potency than TXA. Although there have been isolated case reports suggesting that EACA also causes seizures, there have not been many prospective or retrospective studies associating EACA with postoperative seizures in cardiac surgical patients.

Conclusion:
Tranexamic acid is well established to be efficacious at reducing bleeding, transfusion and re-operation in a variety of clinical settings including cardiac surgery, trauma, orthopedic surgery and postpartum hemorrhage, and guidelines recommend its use based on class 1A levels of evidence and a favorable safety profile. Higher doses have been associated with increased incidence of early postoperative involuntary myoclonic movement or seizure but in the absence of structural brain injury, the long term clinical significance remains unknown.

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ANESTHESIOLOGY 2017
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Will PCC's Replace Plasma Transfusion: Uses and Abuses

Kenichi Tanaka, MD, MSc. **Baltimore, Maryland**

Transfusion of allogeneic plasma has been considered as a standard of care for decades in patients who suffer from hemorrhage after trauma or during major surgery. Plasma transfusion has been commonly administered to patients who are coagulopathic and/or anticoagulated, and are scheduled to undergo invasive procedure or surgery. In 2013, the Food and Drug Administration (FDA) approved clinical use of 4-factor prothrombin complex concentrate (PCC), Kcentra (CSL Behring, Marburg, Germany). Currently approved indications are for the urgent reversal of acquired coagulation factor deficiency due to vitamin K antagonist, e.g., warfarin in adult patients in the settings of (i) acute major bleeding, and (ii) urgent surgery/invasive procedure. There is increasing interest in the use of 4-factor and other PCC products outside these indications. In particular, various PCC products are being considered for the prevention of refractory bleeding after severe trauma,[1] cardiopulmonary bypass (CPB),[2] and for the management of bleeding due to direct oral anticoagulants (DOACs).[3,4] The aims of this lecture are: (i) to discuss differences between plasma and PCC, (ii) to review clinical effects of plasma and PCC, and (iii) to consider practical and safety aspects of using PCC in the perioperative period.

Hemostatic efficacy of plasma transfusion

Muller and colleagues evaluated the effect of plasma transfusion (12 ml/kg, ~3 units) in 38 critically-ill patients with international normalized ratio (median INR) 1.8 (interquartile range, 1.5–2.2) using factor levels, and TG measurements.[5] Prothrombin and factor(F) V, and antithrombin level were increased by about 10%, indicating similar changes in both procoagulant and anticoagulant proteins. After plasma transfusion, INR improved to 1.4 (1.3–1.6), but the peak thrombin level increased only marginally by 6%, and the overall endogenous thrombin potential failed to show clinically relevant improvement.
As relatively small changes in procoagulant factors are expected (i.e., 2–3% per unit), larger volumes of plasma were presumed to be hemostatically more efficacious in the case of major hemorrhage. In the PROPPR (Pragmatic, Randomized, Optimal Platelet and Plasma Ratios) trial, 1:1:1 vs. 1:1:2 ratios of plasma, platelets, and red blood cells (RBC) to major trauma patients were compared for 24-hr and 30-day all cause mortality.[6] Although no difference in the mortality was found between groups, improved hemostasis was more frequently reported in the 1:1:1 group in which larger amounts of plasma-containing products were given (median 19 units of plasma plus platelets vs. 11 units in the 1:1:2 group).[6]

Clinical context of plasma transfusion

In the aforementioned PROPPR trial, acute respiratory distress syndrome and/or pulmonary edema were reported in 13.6% (n=46) of 1:1:1 ratio cohort (n=338) (no specific mention of transfusion-related acute lung injury [TRALI]). Transfusion-associated circulatory overload (TACO) was only reported in 0.3% (n=1). The median dose of plasma was 7 (3–13) units, and the median age of the cohort was 34.5 (25–51). The risk of volume overload is thus small in the major trauma victims who tend to be young males.[6] However, when plasma transfusion (median, 2 units) is given in the setting of warfarin-related bleeding (n=251), TACO was reported in 12% (n=30) while TRALI was reported in 0.8% (n=2).[7] The median age of warfarin-treated patients was 76 (63.6–84.4), and 58.6% were male. It is thus speculated that the risk of plasma transfusion is dependent on the clinical context, and alternative hemostatic strategy should be considered to reduce such risks.

Clinical use of PCC's

Historically, PCC products were clinically used as a replacement for FIX in hemophilia B. PCC's are thus packaged in a vial containing a standard amount of FIX (**Table 1**). Now that specific FIX is feasible, PCC's are not used for hemophilia treatment except for activated PCC (FEIBA; Baxalta, Westlake Village, CA) indicated for patients with FVIII inhibitors.[8]
Therapeutic amounts of FII (prothrombin), FIX, and FX are contained in PCC's, but amounts of FVII, protein C, protein S, antithrombin, and heparin are variable (**Table 1**). Only 4-factor PCC has a labeled indication for acute warfarin reversal as it restores all the vitamin K dependent factors. Efficacy comparison of PCC (n=87) vs. plasma (n=81) for acute warfarin reversal before urgent procedure/surgery demonstrated that PCC was non-inferior to plasma in terms of establishing hemostasis (90% vs. 75% in plasma).[9] PCC achieved a superior INR reduction (INR $\leq$1.3 in 55% of subjects) compared to plasma (10%). Clinical impacts of a lower volume of PCC compared to plasma (mean, 89.7 vs. 819 ml) were evident in the shorter duration of therapy (20.9 min vs. 141 min), the higher factor levels, and the lower incidence of fluid overload (3% vs. 13%; P=0.048).

Timing of dosing PCC may need to be adjusted in the case of CPB, which is associated with extensive hemodilution. Divided doses of PCC before and after CPB may be more practical as shown in a prospective randomized study in warfarin-treated patients undergoing semi-urgent cardiac surgery (n = 40).[10] In this study, a dose of PCC (13.8 ± 2.8 IU/kg) or plasma transfusion (400 ml) was given once before surgery, and once after CPB. In the PCC group, FII and FX levels were both increased to around 50-60% after the first dose of PCC, decreasing INR from 2.7 to 1.2. Factor recoveries from plasma transfusion were much less; FII and FX remained at 20-30% (post-first treatment INR, 1.8). In both groups, factor levels were gradually decreased through CPB, which resulted in prolonged INR (1.6 in PCC group, 2.3 in plasma group) after the second treatment. Additional hemostatic interventions were needed in 6 of 20 in PCC group vs. 20 of 20 in plasma group (P<0.001).
Direct oral anticoagulants (DOACs) are increasingly used as an alternative to warfarin for the prevention of stroke due to non-valvular atrial fibrillation, and for the prevention and treatment of deep venous thrombosis and pulmonary thromboembolism. Idarucizumab (Praxibind, Boehringer Ingelheim, Ridgefield, CT) is available as a specific antidote for dabigatran (Pradaxa, Boehringer

Ingelheim).[11] There is no FDA-approved antidote for direct FXa inhibitors, rivaroxaban, apixaban, and edoxaban, but there are some on the horizon (e.g., andexanet alfa).[12]
Plasma transfusion is ineffective in the DOAC reversal. Off-label uses of PCC's (50 IU/kg) for the management of DOAC-related bleeding are largely based on the limited experiments in healthy volunteers and animals,[13-15] and thus physicians should carefully weigh the risk of bleeding against the risk of thrombosis in each clinical case.

Table 1. Factor contents of different PCC's

	FII IU/ml	FVII IU/ml	FIX IU/ml	FX IU/ml	PC IU/ml	PS IU/ml	Heparin U/ml
4-factor PCC							
Beriplex/Kcentra (CSL Behring, Germany)	20–48	10–25	20–31	22–60	15–45	13–26	0.4–2
Octaplex (Octapharma, Austria)	11–38	9–24	25	18–30	7–31	7–32	<15
Prothromplex Total (Baxter, Austria)	24–45	25	30	30	>20	N.Q.	<15
3-factor PCC							
Bebulin (Baxter, USA)	30	3–5	25	35	N.Q.	N.Q.	3.75
Profilnine (Octapharma, Austria)	37	3	25	16	N.Q.	N.Q.	None
Uman Complex D.I. (Kedrion, Italy)	25	N.Q.	25	20	N.Q.	N.Q.	N.Q

Note: Other PCC products are also available in different countries. PC/PS=protein C/protein S, AT=antithrombin, N.Q.= not quantified, The percent (%) activity of each factor is shown relative to FIX activity (based on the prescribing information for each product; actual factor contents may vary for each vial).

Thrombotic complications associated with PCC's

Some commercial PCC's contain protein C, protein S, antithrombin, and heparin, but their concentrations are lower or minimal compared to procoagulant factors such as prothrombin. The

estimated incidence of thrombosis after PCC is estimated to be 1.4% (95% confidence interval [CI], 0.8-2.1%) according to the meta-analysis involving 1,032 warfarin-treated patients. [16] In perioperative (non-warfarin) patients, decreased procoagulant factors are accompanied by low anticoagulant proteins (e.g., antithrombin). Procoagulant activity of PCC's may be more intense in these patients compared to warfarin-treated patients with normal antithrombin levels. Indeed, higher thromboembolic complication rates were reported in a review of a large healthcare database (2008-2013) regarding the on-label and off-label uses of factor concentrates (n=3801).[17] In patients with congenital factor deficiency, arterial and venous thromboembolic events were reported as 55.6 cases per 1000 exposures for PCC, and 23.8 cases per 1000 exposures for recombinant activated FVII (rFVIIa). However, much higher rates were reported from off-label uses after cardiac surgery; 306 cases per 1000 exposures for PCC, 232 cases per 1000 exposures for rFVIIa.

Conclusions

PCC's are highly effective, and relatively safe hemostatic intervention, particularly in the labeled indication. However, underlying patient condition, and clinical situations can strongly modulate thrombotic potentials. Use of PCC's can be potentially hazardous in certain perioperative conditions, and clinicians should carefully choose optimal hemostatic intervention(s) by analyzing patient's condition and coagulation test results.

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ANESTHESIOLOGY 2017
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Patient Blood Management Cardiac Surgical Patients-Avoiding Anemia and Transfusions
Understanding the Causes of Heparin Resistance

Alan Finley **Columbia, South Carolina**

Of utmost importance to successfully placing a patient on cardiopulmonary bypass (CPB) is maintaining the fluidity of blood after it comes in contact with the CPB circuit. The anticoagulant heparin has long been the anticoagulant of choice to achieve anticoagulation on CPB. Despite the many advantages of heparin, there remains a concern about the significant variability among patients in the anticoagulant effect after receiving heparin. When the responsiveness of the heparin's anticoagulant effect is decreased, the patient is determined to be heparin resistant. Unfortunately, there is no universal definition of heparin resistance in the literature. Broadly, heparin resistance can be defined as the inability of an adequate heparin dose to increase the activated clotting time (ACT) to the desired level. Alternatively, heparin resistance can be defined as a decrease in the heparin dose response.

Much of the concern about heparin resistance revolves around the fact that the minimum ACT to quiet coagulation activation is unknown. This is demonstrated in the wide variability of target ACTs used in the practice. Because the minimum ACT remains unknown, physicians have empirically chosen a target ACT much higher than the theoretical minimum ACT to maintain a margin of safety. At worst, insufficient anticoagulation will result in the development of a catastrophic thrombosis in the CPB circuit or the patient's end organs. At best, inadequate anticoagulation will result in coagulation activation, consumption of coagulation factors, and the development of a consumptive coagulopathy.

Heparin

Heparin has long been used as the anticoagulant of choice for cardiac surgery because it is effective, easy to use, inexpensive, and easily reversed with protamine. However, the response of heparin as measured by the ACT can be highly variable. This high variability can be partially explained by heterogeneity of heparin. Heparin is purified from either bovine or porcine sources and consists of multiple chain lengths with molecular weights varying between 5,000-30,000. Additionally, only 1/3 of heparin molecules posses the critical pentasaccharide sequence to interact with antithrombin (AT) and exert its anticoagulant effect. Finally, the heparin molecule must be atleast 18 saccharides in length to to interact with both AT and thrombin (factor IIa) to form an AT/thrombin/heparin complex. Because of this variability, the United States Pharmacopeia has standards in place to ensure the variability in potency is only +/- 10%.

In addition to the pharmacologic reasons for its variability, the variability in response is also related to biological reasons. After administration, heparin immediately interacts with many substances other than AT. These include heparin binding proteins, endothelial cells, and macrophages and a full discussion of these binding substances is beyond the scope of this summary. If these substances are elevated in the patient, there interactions with heparin may result in lower than expected heparin concentrations and decrease the heparin responsiveness.

Monitoring

Due to the large variability in heparin, the anticoagulant effect of heparin is routinely monitored to ensure therapeutic anticoagulation has been achieved. The most common method of monitoring heparin's anticoagulant effect is the ACT. The ACT was adopted in cardiac surgery because it is easy to use as a point of care test and unlike the activated partial thromboplastin time, is not made unclottable by the high concentrations of heparin achieved during cardiac surgery. However, the ACT is a rather crude test that is not specific to heparin's anticoagulant effect on thrombin (see Table 1).

Table 1. Factors Affecting ACT

- Hypothermia
- Hemodilution
- Medications
    - Heparin
    - Warfarin

  - Aprotinin (celite more likely than kaolin)
  - Platelet Inhibitors (therapeutic medications like cyclooxygenase inhibitors, IIb/IIIa or ADP inhibitors, or antiplatelet antibodies)
  - Direct thrombin inhibitors (e.g. hirudin derivatives, argatroban)
  - Protamine
- Thrombocytopenia or Thrombocytosis
- Factor Deficiencies (any contact or common pathway coagulation factor)
  - Contact factors (Factor XII/Factor XI, kallekrein) or intrinsic (Factor VIII)
  - AT III
  - Common pathway: (Factor V, II)
  - Fibrinogen
- Disease States: Anticardiolipin/antiphospholipid antibodies

Many of these factors are commonly seen during cardiac surgery and should raise the concern that other factors are involved when the target ACT is not achieved.

An alternative method of monitoring the anticoagulant effect of heparin is the heparin dose response curve. This curve allows for quantification of the heparin responsiveness of each individual patient. To plot a heparin dose response curve two ACTs should be performed, a baseline ACT with no heparin present and an additional ACT after a known heparin concentration has been added to an in vitro blood sample. A curve can then be plotted and the slope of the curve can be calculated by the equation:

$$\text{Heparin Sensitivity} = \frac{(\text{ACT after Heparin} - \text{Baseline ACT})}{\text{Heparin Concentration}}$$

Alternatively, the heparin sensitivity index can be calculated following an in vivo heparin bolus by substituting the heparin-loading dose for the heparin concentration in the above equation. Although the heparin dose response curve is an attempt to overcome some of the individual variability of heparin responsiveness, it fails to predict the heparin concentration after the loading dose. This is likely explained by the absence of some heparin binding proteins in the in vitro calculated heparin sensitivity and the lack of accuracy in estimating the patients blood volume.

Mechanism

Traditionally, heparin resistance has been attributed to AT deficiency. This seems logical given that heparin exerts its anticoagulant effect indirectly through AT and thus deficiency of AT would diminish heparin's anticoagulant effect. Both in vitro and in vivo studies have confirmed that low AT levels decrease heparin responsiveness. However, the correlation between the AT level and heparin dose response is low. Additionally, not all heparin resistant patients that receive AT concentrate show an increase in heparin responsiveness. Thus, there must also be a non-AT dependent mechanism for heparin resistance. Patients who have a normal baseline AT level are fall into this category and have an AT independent mechanism.

Treatment

When faced with heparin resistance, clinicians have four treatment options available to them. The first option is to administer additional heparin to account for the potential of excessive heparin binding proteins. Ideally, one would be able to monitor point-of-care whole heparin concentrations to ensure adequate heparin dosing. Monitoring heparin concentrations also has the benefit of avoiding excessively high heparin concentrations, as there is a ceiling effect on heparin's anticoagulant effect. Furthermore, a high heparin concentration increases the risk of heparin rebound in the postoperative period and should be monitored for when higher doses of heparin have been administered.

The second treatment option for heparin resistance is AT supplementation with fresh frozen plasma. This has historically been the source of AT used to treat AT dependent heparin resistance. However, evidence supporting this treatment option is lacking with only case reports and 1 small retrospective study to support its use. The standard dose of FFP for heparin resistance is 2 units (1 u AT is present in 1 mL FFP or ~ 500 units of AT in 2 units FFP), which is only expected to increase the AT by 2-3% per unit. Although this does result in an increase in AT

levels, such a small increase is unlikely to have a clinical impact. This has been confirmed in the literature as using 2 units of FFP failed to increase the ACT.

An alternative method of AT supplementation is with AT concentrates and because the AT dose is more concentrated than FFP, results in a much greater increase in AT concentration. Furthermore, studies have demonstrated a consistent increase in the ACT after its administration. However, the literature is confusing in regards to the dose used to treat heparin resistance. The traditional dose is ~500-1000 units, but many recent studies have used doses as high as 75 units/kg (7500 units for a 100 kg patient). Such high doses confuse the results of the study as these high doses maintain AT near normal levels throughout cardiopulmonary bypass, which is not normally the case during cardiac surgery. This is a major confounding factor when interpreting these studies as the decrease in coagulation activation seen during surgery might be related to a separate mechanism other than the treatment of heparin resistance. Nonetheless, the STS/SCA blood conservation guidelines still recommend the use of AT concentrate for AT dependent heparin resistance as a method to decrease FFP transfusion before cardiopulmonary bypass. A closer look at the study leading to this recommendation reveals that the design of the study played a major role in this conclusion. In this study, heparin resistant patients received either AT concentrate or placebo. As has been demonstrated in multiple studies, the AT concentrate group had an increase in their ACT and thus proceeded with cardiopulmonary bypass. As one would expect the placebo group showed no change in the ACT and the study protocol dictated that they receive 2 units of FFP. This one difference accounted for the vast majority of the intraoperative difference seen in FFP transfusions. Furthermore, the AT concentrate group received more FFP in the postoperative period because of higher chest tube outputs.

The last therapeutic option would be to accept the current ACT and commence cardiopulmonary bypass. This option if often not chosen for fear of inadequate anticoagulation. However, there is some evidence that clinicians could in fact chose this option in many situations without negative sequalae for their patients. First, there is wide variability in the target ACTs used in clinical practice with some institutions using target ACTs as low as 350 seconds with good results. This suggests that many are using a target ACT that is higher than necessary to safely conduct cardiopulmonary bypass and heparin resistance may be partially related to choosing too high of a target ACT goal. Additionally, the evidence supporting the routine use of ACT monitoring does not consistently support a benefit with its use.

Conclusions

Heparin resistance is a complex, multifactorial disorder. It is complicated by the fact that heparin's anticoagulant effect is widely variable and the monitoring most commonly used, the ACT, is not specific to heparin. Furthermore, the mechanism of decreased heparin responsiveness is complex and not always dependent upon AT. Because of this, clinicians should attempt to minimize empiric treatments. A point of care whole blood heparin concentration will provide clinicians the ability to rule out excessive heparin binding proteins. Although no studies support obtaining preoperative AT concentrations, this strategy may be beneficial in certain patient populations who are at higher risk of developing an acquired AT deficiency. Knowing the AT concentration has the benefit of avoiding the administration of AT concentrate, which would not only be expensive, but also ineffective if the AT concentration is within normal limits. Much remains unknown about the best strategy for managing these patients and future research is needed to confirm a clinical benefit of the treatment options often chosen.

ANESTHESIOLOGY 2017
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Should Transfusion Be Considered a Quality Metric?

Gregory M. Janelle, MD FASE **Gainesville, FL**

In order to answer this question, it is probably appropriate to have some background information on the definitions, applications, and development of Quality Measures in general. Centers for Medicare and Medicaid Services (CMS) reprioritized volume-based care toward value-based care in the last decade in part as a response to massive escalations in US healthcare spending. As part of this national endeavor, there has been a push toward a reimbursement system based on maintaining safety while improving value for patients through reorganization of care around medical conditions and treatments, incorporating mandatory measurement and public sharing of specific healthcare related outcomes in part via the use of electronic health records and national reporting systems.[1]

CMS programs were subsequently devised to incentivize or penalize hospital systems for their ability to achieve value-based purchasing. Examples of these initiatives include 1) bundled payments, where certain diagnosis related groups (DRGs) are allotted comprehensive lump-sum payments for the entire procedure and recovery (e.g. total joint replacements) and 2) programs which apply penalties for costly events, such as readmissions or for hospital acquired conditions (CAUTI, CLABSI, etc.) based on performance compared to a national average. These models, rather than simply incentivizing throughput, result in hospital and physician margins that in turn are determined by their ability to deliver services for reduced charges with less complications.

Quality Measures in this context are essentially tools that help measure or quantify healthcare processes, outcomes, patient perceptions, and organizational structure and/or systems that are associated with the ability to provide high-quality health care and/or that relate to one or more quality goals for health care.[2] These goals include effective, safe, efficient, patient-centered, equitable, and timely care.[2] The world of relevant acronyms for quality measures, their application, and their reporting can be quite daunting. As such, a brief guide is provided below:

Acronyms Relevant to Anesthesiology Quality Metrics

APMs: Advanced Alternative Payment Models
AQI: Anesthesia Quality Institute
CHIPS: Children's Health Insurance Program
CJR: Comprehensive Care for Joint Replacement
CMS: Centers for Medicare and Medicaid Services
CPI: Continuous Performance Improvement
DRG: Diagnosis related groups
HCAHPS: Hospital Consumer Assessment of Healthcare Providers and Systems
MIPS: Merit-based Incentive Payment System (through NACOR)
- Four Performance Categories:
  - Quality
  - Clinical Practice Improvement activities (or Improvement activities
  - Meaningful use of certified electronic health record (HER) technology (referred to as "advancing care information")
  - Resource use (cost)

MACRA: Medicare Access and CHIP Reauthorization Act of 2015
NACOR: National Anesthesia Clinical Outcomes Registry
PQRS: Physician Quality Reporting System
QCDR: Qualified Clinical Data Registry; Exist under MIPS as a method of data submission
QR: Qualified Registry, another method of data submission for MIPS but limited to measures within the Quality Payment Program
TEP: Technical Expert Panel

A standardized approach for quality measure development and management is in place for CMS.[2] The steps include:

1. Measure Conceptualization
2. Measure Specification
3. Measure Testing
4. Measure Implementation
5. Measure Use, Continuing Evaluation and Maintenance.

A Technical Expert Panel (TEP) is convened for each of steps 1-3. After the initial gap analysis is developed, the TEP submits the measure to CMS for approval. Step 2 includes feasibility studies, a business analysis, as well as public posting for comment. In Step 3, the measure undergoes testing, following which the results are again posted for public review. As part of the Measure Implementation in Step 4, all measures under consideration are posted, reviewed by a Measures Application Partnership for review, and receive a consensus for implementation. As part of Step 5, the impact, effectiveness, and efficiency of the measure is assessed, re-evaluated for revision and/or improvement, and aggregate date is reported.

At this point, many Quality Measures related to the care of patients with cardiac disease have been implemented. These include, but are not limited, to benchmark times for fibrinolytic therapy and primary percutaneous coronary interventions for acute myocardial infarction (AMI), 0600 glucose measurements post-operative day 1 from cardiac surgery (no longer in place from 2016 onward), continuation of perioperative beta-blockers for patients on prior beta-blocker therapy, central line associated bloodstream infections, catheter-associated urinary tract infections, HCAHPS patient satisfaction measures, and same-day institution of beta-blocker therapy in CABG patients. Recently, CMS announced plans to implement bundled payments for CABG and AMI, coming on the heels of the CJR program, with a planned launch date of July, 2017, for an estimated 1120 hospitals.[3]

With respect to transfusion practices, few would argue that there is no room for improvement. Approximately 10% of all hospital admissions undergoing any invasive procedure receive blood for a variety of perhaps untested or unproven indications, and the direct costs associated with the over 14,000,000 units of packed red blood cells (PRBCs) alone in the U.S. annually are staggering even ignoring the costs of associated complications. In a recent review of nearly 500 published articles, only 12% of PRBC transfusions in 450 typical inpatient medical, trauma, or surgical scenarios were deemed "appropriate" by a panel of 15 experts.[4] While anemia is potentially dangerous, the combination of anemia, bleeding, and transfusion portends significant increases in morbidity and mortality across a number of different patient populations, including those undergoing cardiac surgery.[5-8] Still others have demonstrated equivalence, non-inferiority, or superiority of restrictive transfusion practices, although more context-specific applications may yield conflicting data.[9-12]

The Society of Thoracic Surgeons and Society of Cardiac Anesthesiologists have published revised blood conservation clinical practice guidelines, including 72 recommendations, of which 13 represent class I interventions.[13] Unfortunately, the penetrance of guidelines across our specialty is lacking, with only 26% of anesthesiologists incorporating 1 or more change to their practice from the recommendations.[14] Not surprisingly, transfusion practices in cardiac surgery vary drastically, as evidenced by a report from Benette-Guerrero et al. of over 100,000 CABG patients from nearly 800 US sites demonstrating PRBC transfusion rates ranging from 7.8-92.8%, plasma transfusion rates from 0-97.5%, and platelet transfusion rates from 0.4-90.4%.[15]

Early evidence suggests that implementation of value based care results in substantial measurable improvements in composite measures of quality.[16] In CABG surgery, a multicenter quality collaborative in Michigan initiated a focus on blood conservation as a quality metric that achieved significant reductions in RBC, FFP, and platelet use with concomitant reductions in rates of surgical site infection, reoperation, renal failure, prolonged ventilation, and ICU duration.[17] Similarly:

1. Eastern Maine Medical Center demonstrated a 2.6-day reduction in length of stay and $4000 per patient reduction from a blood conservation initiative[18]
2. The University of Kentucky demonstrated an overall reduction in transfusions by reducing their hospital-wide transfusion trigger from 8gm/dL to 7gm/dL. Between years 2010-2012, 4492 units of RBCs were saved at a total product savings of $943,320.00 and an activity based cost savings of $5,314,036.00.[19]

3. Stanford University reported implementation of real-time clinical decision support and best practice alerts that reduced overall RBCs transfusion rates from 2009-2012, resulting in a savings of $1,616,750.00. [20]

The Anesthesia Quality Institute's (AQI) National Anesthesia Clinical Outcomes Registry (NACOR) has been approved as a Qualified Clinical Data Registry (QCDR), as well as a Qualified Registry (QR) for 2017 by the Centers for Medicare & Medicaid Services (CMS).[21] NACOR quality reporting is complementary to ASA members, may be utilized individually or by group practice, and allows for reporting of Quality and Improvement Activities components under the Merit-based Incentive Payment System (MIPS). In addition to MIPS, non-MIPS QCDR quality measures are supported. Recently approved in June, 2017, one of these non-MIPS QCDR Measures reads, "Adherence to Blood Conservation Guidelines for Cardiac Operations Using Cardiopulmonary Bypass-Composite."[22] This QCDR is the result of a TEP's recommendations to the ASA Committee on Performance and Outcomes Management, and includes the following strategies:

1. Use of lysine analogues, unless contraindicated.
2. Use of mini-circuits or retrograde autologous priming or ultrafiltration
3. Use of red cell salvage using centrifugation
4. Use of transfusion algorithm supplemented with point-of-care testing

The performance measure is met in patients over the age of 18 undergoing non-emergent cardiac surgical procedures using cardiopulmonary bypass for whom a cumulative score of 100% of blood conservation strategies are employed.

In order to facilitate compliance, the SCA Blood Conservation Working Group's CPI task force will be publishing a Summary Statement on Blood Conservation and Transfusion in Cardiac Surgery along with a Cardiac Surgery Hemostasis Algorithm, both with and without viscoelastic point-of-care testing.

In summary, the question as to whether or not transfusion in cardiac surgery should be a quality measure has been answered for us!

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ANESTHESIOLOGY 2017
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Electrophysiology for the Practicing Anesthesiologist

Jacques Neelankavil, MD — **Los Angeles, CA**
Alina Nicoara, MD — **Raleigh, NC**

Introduction

Cardiac arrhythmias account for over 881 000 hospitalizations and 40 700 deaths per year in the USA, with a total of roughly 14.4 million patients affected by such conditions [1]. Many of these patients require diagnostic or therapeutic intervention in an electrophysiology laboratory with involvement of an anesthesiologist. Implantation of an artificial permanent pacemaker for bradyarrhythmias, or an implantable cardioverter/defibrillator (ICD) for lethal tachyarrhythmias has been shown to significantly reduce morbidity and mortality [2]. Perhaps the most important advance in the field of electrophysiology over the past decade is development of the therapeutic electrophysiology study, sparing many patients the need for potentially toxic drugs or cardiac surgery. As electrophysiology intervention comprises cardiac optimization for these patients, the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines do not apply for these procedures. Therefore, sophisticated understanding of the mechanisms behind various arrhythmias, specific procedures performed for diagnosis and treatment, and associated risks is essential if the anesthesiologist is to safely care for this unique patient population

Catheter Ablations

Programmed electrical stimulation with simultaneous recording of intracardiac signals was first performed in 1971 [3], and is the basis of the modern, diagnostic electrophysiology study. Once it became evident that transvenous electrophysiology study could identify mechanisms of tachycardia and localize arrhythmogenic foci, catheter-based ablation techniques soon followed. Although high-voltage direct current was originally used, radio frequency current is now preferred, and catheter ablation has become first-line therapy for many tachyarrhythmias

Electrophysiology studies and catheter ablations are performed in dedicated electrophysiology laboratories. Access is typically via the femoral vein, but subclavian, internal jugular, or brachial approaches are also used to introduce electrode catheters. If the left heart is instrumented, it is approached by either a transseptal or retrograde aortic approach, and systemic heparinization is used to prevent systemic thromboembolism. Once the electrode catheters are placed, initial baseline recordings are followed by burst pacing at various fixed cycle lengths, as well as programmed electrical stimulation (PES), with or without catecholamine infusion. PES consists of multiple delivered stimuli at a fixed cycle length (e.g., eight beats at a rate of 100 beats/min), followed by a beat that is moved earlier and earlier, until it falls within the tissue's refractory period, which can induce arrhythmias, thus allowing definitive diagnosis of arrhythmia mechanism

Cardiac mapping identifies the temporal–spatial distribution of electrical impulses generated by the myocardium during both normal and abnormal rhythms. Various mapping techniques are available to identify sites for which radio frequency ablation can be curatively applied

Regardless of mapping technique, once an arrhythmogenic focus is successfully localized, ablation is performed using low-voltage, high-frequency radio frequency energy (100 kHz to 1.5 MHz). Temperatures above 90°C produce a high-impedance barrier of denatured tissue protein at the catheter tip, which increases the risk of thromboembolism. Catheters with saline-cooled tips can decrease formation of this coagulum, thus allowing production of larger radio frequency lesions with lower risk of thromboembolism [4,5]. Cryothermal energy may overcome other disadvantages of radio frequency, such as tissue disruption at excessively high temperatures and nonuniform lesions [6,7]. Subxyphoid access for epicardial mapping and ablation has shown success in certain

arrhythmias refractory to endocardial ablation [8,9]. Wider application of this technique may be possible, but is currently only performed at a small number of specialized referral centers

Complications

Electrophysiology studies and catheter ablations are generally safe, but do carry definite risk [10,11] Most complications are related to the vascular access (3–4%), including bleeding, infection, hematoma, and vascular injury. Intracardiac catheter placement and PES can lead to hemodynamically unstable rhythms requiring direct current shock. Cardiac perforation with tamponade and complete heart block requiring pacemaker placement occur in less than 1–2% of radio frequency ablation cases. Risks specific to pulmonary vein isolation include pulmonary vein stenosis and atrioesophageal fistula (0.01–0.2%) [12,13]. Rarer complications for all intracardiac radio frequency procedures include valve damage, systemic embolization, and stroke (<1% when the left heart is accessed), phrenic nerve injury, and radiation skin burn. Death due to complications is exceedingly rare (0.1–0.3%). Predictors for complication include structural heart disease and ablating more than one target [14]

Anesthetic Management

The patient population requiring EP procedures can vary from healthy young patients who present for ablation of an AV-nodal reentry tachycardia, to patients with left ventricular assist devices for end-stage heart failure and multiple comorbidities who present for VT ablation. Understanding the complexity of the patient population and documenting a thorough patient history will significantly improve administration, efficacy, and safety of the anesthesia [15]. Electrophysiology studies and catheter ablations are most commonly performed on an elective basis, but are sometimes carried out urgently, usually in cases of recurrent, unstable ventricular tachycardia. For most types of arrhythmias, sedation via propofol infusion is usually adequate. However, ablation of complex atrial fibrillation can be time-consuming (6–8 h), and carries the risk of atrioesophageal fistula. This may be reduced by using oral contrast via an orogastric tube placed at the gastroesophageal junction [16]. General anesthesia with endotracheal intubation is indicated when oral contrast is used, but as inadvertent phrenic nerve stimulation with pacing can lead to phrenic nerve damage, neuromuscular blockader should be avoided. General anesthesia is also indicated for ablation of destabilizing monomorphic ventricular tachycardia in patients with ischemic heart disease. Esophageal temperature should be monitored for conductive heat transfer to the esophagus, which may cause esophageal injury, and possible transmural tissue necrosis, mediastinitis, and a fistulous connection between the esophageal lumen and the left atrium (atrio-esophageal fistula). Rapid elevation of esophageal luminal temperature (> 0.05°C-0.1°C/second) may indicate efficient transfer of heat to the esophagus due to a combination of catheter orientation, catheter contact, and minimal or absent intervening connective tissue between the left atrium and the esophagus [15].

Aside from standard monitors, the need for invasive arterial monitoring is dictated by patient comorbidity. Temperature monitoring is indicated for longer procedures; monitoring esophageal temperature can reduce the risk of atrioesophageal fistula while ablating atrial fibrillation [17]. Adhesive surface defibrillator/pacing pads should be applied in all cases, and a functional defibrillator readily available. Transesophageal echocardiography is performed to rule out intracardiac thrombus in patients with atrial fibrillation and atrial flutter. Precautions against intravenous air should be taken to prevent paradoxical embolism during trans-septal puncture. When indicated, systemic heparinization is monitored with a targeted activated clotting time greater than 300 s. Catheter tip irrigation fluid should be accounted for when calculating total fluid administration and the urinary bladder should be catheterized to monitor urine output for prolonged procedures. The upper and lower extremities should be properly supported to avoid injury due to positioning and from multiple electrical wires near the patient

Ventilation practices during cardiac ablation can range from conventional to extremely unconventional. Realistic expectations regarding safety and efficacy of various ventilation modes must be clearly discussed and agreed upon before the start of the case. Data on the role of individual anesthetics in EP procedures are limited since patients generally receive a combination of drugs. Anxiolytics, such as midazolam, and opioids, such as fentanyl, are used to facilitate sedation. Intravenous anesthetics, eg, propofol, ketamine, etomidate, and dexmedetomidine, can be used for induction or maintenance of general anesthesia [15].

While inducing arrhythmias and mapping, transient hemodynamic instability commonly occurs. Inotropes/vasopressors may help maintain hemodynamic stability. In such cases, clear and open communication with the cardiologist is essential for achieving safe and successful mapping. Cardiac perforation leading to tamponade must be ruled out in the presence of significant hypotension. Emergency airway access may be obstructed by fluoroscopy equipment. Radiation exposure should be minimized by using pulsed fluoroscopy and protective barriers.

The Environment of the Electrophysiology Laboratory

Understanding the progress of various stages and the potential complications for EP procedures is just as important as it is for surgical procedures. Observation of the progression of the catheter placement on the fluoroscopy monitors, general knowledge of the steps of the EP procedures, and close communication with the electrophysiologist, EP registered nurse, or technology representative will help to ensure the timely anticipation of anesthetic needs. Recent studies in patient safety in cardiac surgery have shown that breakdowns in teamwork lead to operative flow disruption and technical errors. Even if they are minor, disruptions may impact the ability of the team to manage major events, and may lead to adverse events and compromise patient safety [18-21]. Recently, interventions designed to improve teamwork, such as team training, structured communication tools, and protocols, have been implemented in the cardiac operating room. In addition to timeouts and checklists, communication tools such as surgical briefings and debriefings have given an opportunity for the entire operating room staff to establish a dialogue focused on the unique aspects and requirements of the procedure performed. The EP procedure room is an equally complex environment in which caregivers from different specialties interact and use highly sophisticated equipment to care for patients with significant comorbidities. While timeouts and checklists have been introduced and are used in EP procedure rooms, other communication tools such as briefings and debriefings, or team training programs have not been implemented, and to our knowledge, the impact of such tools and programs on patient safety in the EP procedure room has not been investigated.

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ANESTHESIOLOGY 2017
BOSTON OCTOBER 21-25

MACRAs Physician-Focused Alternative Payment Model (PF-APM) Options: A Multispecialty Perspective

BACKDROP

The Medicare Access and Chip Reauthorization Act (MACRA) replaced the Sustainable Growth Rate (SGR), which had been renewed numerous times with a series of patches. MACRA created two options for compliance. The first path, which does not require assumption of insurance risks, is the Merit-based Incentive Payment System (MIPS) that consolidated existing quality programs and added clinical practice improvement. The other fork in the new highway is the Alternative Payment Model (APM) with one subgroup variant being Physician Focused (PF-APM) where the physician accepts some level of risk for services and expenses over which they have some control. One should be aware that another variant is the Hospital Focused (HF-APM), but this presentation is focused on PF-APMs with an emphasis on potential multispecialty models that in a particular community enable anesthesiology practices to participate; so the goal of this presentation is to increase awareness of subtle opportunities that may be developed by others in the community where anesthesia may play a role. Other presentations at this meeting will focus on more anesthesia specific options (e.g., Perioperative Surgical Home). While physicians may have a wide range of experience with the MIPS elements, most have (at a minimum) a grasp of the basic concepts and foundations. In contrast at the other end of the numerical spectrum, few physicians have any idea how APMs might apply to their practice. Some APM options such as the Patient Centered Medical Home have been around for some time yet have not penetrated the market in many parts of the country, especially in smaller practices that may lack infrastructure or feel they have too many immediate production pressures to take the time to apply the concept.

Our current system is oriented towards intervention and is often focused on the anecdotal, and what is possible, while emerging models emphasize prevention and evidence-based or experientially-based utility. Neither camp wants to harm patients; they just have a different idea of how to get there. The HMOs of the 90s were viewed as being solely focused on finances (Just say no!), and the models now under discussion are focused on balancing optimization of outcomes, costs, and patient satisfaction. While we may do a great job of diagnosing, managing, and treatment of chronic diseases, we do not do as well preventing their development, managing or preventing their complications, and differentiating the efficacy of various options. There are multiple reasons. There ae silos of care where the emphasis on focused on the part a particular physician or specialty may play. There may be disconnects between the consumer (the patient) and the producer (not limited to physicians) so questions of costs and utility are often not asked. Does the test need to be done? Before one commits to a procedure, the questions of how often it meets expectations, at what costs, and at what risks are not valued by the current system. Additionally, there is no prerequisite that the patient has an affirmative responsibility to optimize their personal health. And finally, the system itself is a barrier.

BARRIERS

The driving concepts behind APM begin with the realization that existing models do not address barriers to redesigning services that provide a higher-value of healthcare. Before one can innovate, they must have the latitude to reallocate precious, but limited, resources and have space to make the transition. Two commonly mentioned barriers are either no or inadequate payment for many high value services and financial penalties for delivering a different mix of services that result in a lower costs to society.

There are many services that may benefit patients either through enhanced personal time in an alternative model or the freedom to pursue lower cost options with improved or neutral outcomes. We are not paid to take the time to counsel patients on lifestyle and the various options available to them that are time- intensive or require relational databases that may not exist and would be expensive to establish. Physicians are best positioned to evaluate alternative delivery systems, optimize cost delivery settings, and different combinations of services and providers. But that takes time, requires support resources (human and financial capital) that are not made available currently, and alignment of incentives that focus more on outcome, utility, and coordination rather than component production and what is merely possible.

During the transition from the current model to the emerging models, one still has to keep the doors open; this is one laudable goal not supported by United Way! If the current transactional practice revenue decreases by delivering fewer or lower cost services, a transitional strategy will be necessary to shield operating losses since the changes will not likely be proportional and may be even be higher in a temporary dual system.

There are a number of examples where no or inadequate payment for high-value services are a barrier by both Medicare and private health plans for services that would benefit patients and help reduce avoidable spending. For example, responding to a phone call about a symptom or problem might help patients avoid a more expensive ER visit. There is no recognition for the value of coordination between primary care physicians and specialists or taking ownership for the coordination of care and time spent to avoid ordering duplicate tests and prescribing conflicting medications. There are no incentives for the time that it takes community and emergency physicians to facilitate discharge planning in emergency departments that could enable patients to be safely discharged without hospitalization. Some high-risk patients might respond to a proactive early-stage telephone call that would optimize preventive care and lower comorbidities. Deconditioned patients in particular, and many patients in general, would benefit from prehabilitation but there is no support for development of this intervention. Smoking cessation reduces respiratory complications and length of stay as well as improvement in wound dehiscence. Current paradigms do not recognize these benefits while a well-designed APM would embrace such opportunities.

There are several ways that financial penalties for delivering a different mix of services may pose a transitional risk to physicians. As the health of patients improve, they will require fewer services and may avoid developing a disease. They would be expected to have fewer complications or lower comorbidities that require intervention. Even though there may be fewer or less costly procedures, the cost of running a practice generally does not decrease; rent and utilities are not pegged to quality of care or resource utilization. Since most of the savings to the system from APMs do not come from physician payments, the savings can be realized without financially targeting and implicit penalization of physician practices for delivering a societal goal. With healthier patients, physician practices would receive less income under current approaches. This could be the greatest conflict with our current FFS system, and one essential foundation and question that must be answered if we are to make substantial progress as APM options are developed.

With these barriers, what are the prerequisites for successfully creating new options? The Center for Healthcare Quality and Reform has identified three characteristics for enabling change:

1. Flexibility in Care Delivery
   In order to overcome the barriers discussed above, an APM must provide enough innovative flexibility—with a patient centric focus—to deliver a mix of services that makes sense but is not covered within today's payment methodologies so that we can provide a new path to efficiency and effectiveness.

2. Adequacy and Predictability of Payment
   As one contemplates navigating the coming changes, this characteristic is essential so that the financial resources will be available to start the process with confidence that the return on investment (ROI) will be there. The fear at the end of the dance is that we will be out there alone. If we are successful, there is a concern that some politician will award our victory to a political crony. So the rules of engagement must deliver adequate and predictable resources to allow physicians to create the alternative structures that will identify high-quality service opportunities whose costs include both start-up and transitional financial risk to physicians. The exposure must be both risk-adjusted to recover their investment yet be within an acceptable financial risk corridor for small businesses and medical practices.

3. Accountability for Costs and Quality That Physicians Can Control
   The program design must be structured to assure non-provider stakeholders, (patients and payers) that the outlays will be controlled or reduced with the implicit assumption that quality will at a minimum be maintained if not improved. However, the beauty of the "Physician-Focused Payment

Models" is that individual physicians should only be at risk for those aspects of spending and quality they can materially control or influence. This is similar to Activity-Based Accounting where one has to have control over the activity for it to be in that cost center.

EXAMPLES OF POTENTIAL MODELS

In the document A Guide to Physician-Focused Alternative Payment Model prepared by the AMA and the Center for Healthcare Quality and Payment Reform, they identify seven potential models. Since this is an emerging concept and there are no other resources that synthesize the material as well as this publication, I will rely upon the following excerpts from that comprehensive document to stimulate your evaluation of how one of these models could benefit your practice and your community:

"APM #1: Payment for High Value Services where physicians are paid for delivering desirable services that are not currently billable in order to avoid the need for patients to receive other, more expensive services… A physician practice would bill and be paid for the time and resources needed to apply appropriate use criteria and engage in an education/shared decision-making process with patients in order to determine the most appropriate diagnostic tests to use… In contrast to a typical shared savings program, an individual physician practice's payments would not be explicitly tied to how much money that practice saved the payer. Instead, the physician practice would be paid adequately to deliver appropriate services, and the payer would save money by spending less on avoidable services (for the patients in all participating practices)." Could such a program be a component of an early stage PSH (e.g., pre-op testing protocols, prehabilitation, smoking cessation)?

"APM #2: Condition-Based Payment for Physician's Services … where a physician has the flexibility to use the most appropriate diagnostic or treatment option for a patient's condition without reducing the operating margins of the physician's practice… the practice would have the flexibility to use the payments for whatever combination of services were most effective –office visits, phone calls, emails, support from non-physician staff, etc." These would replace E&M codes limitations with monthly payments targeted to chronic conditions. For a primary care physician with global risk, potentially a seamless transition into a PSH may become an opportunity or smoking cessation achieved as a result of a PSH may enhance the management of a COPD patient.

"APM #3: Multi-physician Bundled Payment…where the goal is to give multiple physicians who are providing services to the same patient the flexibility and resources needed to redesign their services in coordinated ways that will improve quality and reduce the costs of diagnosis or treatment… Patients would benefit because the physicians delivering their care could work together in a more coordinated way and use the additional resources and/or flexibility under the bundled payment to deliver different types or combinations of services that cannot currently be provided. The payer would benefit because the new payment would enable the physicians to deliver care more efficiently, order fewer or lower-cost services from other providers, and/or reduce the number of complications for their patients. The physician practices would benefit by having the resources and flexibility to deliver the most appropriate services to patients in a coordinated way without concern about which services will generate more revenue for the individual practice." This model has a very high potential as well as likelihood for participation by anesthesiologists since it offers major benefits and aligns incentives for all stakeholders to coordinate care by virtue of shared risks and rewards. This model would allow acceptance of risks for professional services, especially in circumstances where the facility partner is unable or unwilling to participate.

APM #4: Physician-Facility Procedure Bundle… where the goal is to give physicians greater ability to choose the most appropriate hospital or other facility to deliver a particular procedure and to work with the facility to improve efficiency and quality in delivering that procedure...The patient would benefit by being able to receive high quality care at the lowest-cost facility and to receive coordinated and efficient care from the physician and facility staff. The payer would benefit because the Alternative Payment Entity could accept a lower payment for the bundle than the total amounts that would have been paid separately to the physician and facility under current payment systems. The physician practice could benefit by using the bundled payment to cover the costs of services that are not current billable or do not receive adequate compensation,

and by receiving compensation for changes in the physician's services that reduce the costs of the services delivered by the facility." This model has a very high potential as well as likelihood for participation by anesthesiologists since it offers major benefits and aligns incentives for all stakeholders for both surgical and obstetrical management. I would note that the marked variability in hospital charges will be a significant driver and an opportunity to engage payers in many communities. Since anesthesiologists may cover multiple sites and know the inside baseball, they may be in a unique position to help select the most efficient or progressive facilities (e.g. stable facilities with good policies and procedures versus one with high turnover and poor/unenforced policies).

APM #5: Warrantied Payment for Physician Services…where the goal is to give physicians adequate payment and flexibility to redesign care in a way that will prevent complications and reduce the spending needed to treat them… In contrast to penalties that reduce payments when complications occur, the warranty approach provides greater upfront resources so that care can be redesigned to reduce complications. In addition, although no additional payment is made when complications occur, the cost of treating some complications is built into the warrantied payment amount, so the physician practice is not financially penalized when a small number of complications occur, but it is rewarded if it can eliminate most or all complications." This could be a potential variant of a monetization strategy for a PSH.

APM #6: Episode Payment for a Procedure… where the goal is to give physicians and other providers the ability to deliver all of the care during and after delivery of a particular procedure or treatment in a coordinated, efficient way… all of the costs involved in performing hip or knee surgery during an inpatient hospital admission, delivering rehabilitation services after surgery, and treating any post-operative complications. The payment amount would be higher for patients with comorbidities and functional limitations that would require more inpatient or post-acute care. The payment amount would be adjusted based on measures of quality and outcomes for the patients." This essentially takes Models 4 and 5 plus adds the post-discharge management and re-admission risk components. While optimally this might be a later more mature option after experience in Models 4 and 5, market and political pressures may make this the initial option. The current Comprehensive Care Joint Replacement (CJR) has some of the elements of this APM but it is currently limited to hospitals. It could be revised so that the episodes could be managed by physicians ; however, at the time of this draft, it is *not* on the APM list under the proposed rules!

APM #7: Condition-Based Payment… gives physicians and other providers who are delivering care to patients for an acute or chronic condition the flexibility and accountability to deliver the most appropriate treatment for the patient's condition in a coordinated, efficient, high-quality manner." One of the examples was for a Condition-Based Payment for Post-Acute Care Following a Hospitalization for spine surgery. This model may be a separate initiative, perhaps with different provider groups, as either an early stand-alone or as an independent but complementary part of Model 3 or 4, but an integral part of Model 6. The post-discharge management of a PSH patient could be a stand-alone approach in some communities and circumstances. In the procedural arena, I do not see this as a long term option and would predict a rapid integration with one of the other models.

CHANGES PROPOSED FOR 2018

While most of the 2018 changes are in the MIPS bucket, there are some that apply to the APM realm. The requirement that practices bear "more than nominal risk" for monetary losses is defined as the lesser of 8% of total Medicare revenues or 3% of total Medicare expenditures, and the 2018 proposal would extend that standard for 2 more years. There had been discussion of increasing this to 15% so this was good news. There were 11 proposals submitted to PTAC, of which 3 were reviewed and accepted at April meeting. The ACS-Brandeis Advanced APM was submitted by the American College of Surgeons was accepted and is very applicable to anesthesiologists. The link to their website and a deeper dive is: https://aspe.hhs.gov/system/files/pdf/253406/TheACSBrandeisAdvancedAPM-ACS.pdf. This model has the highest potential to relate to anesthesia at this point in time. However, now is the time to pursue one of the seven models above and evaluate your options for the future.

IN CONCLUSION

As this document is updated in August, we are in the current phase of rule-making and the ASA and AMA have several units diligently studying options to preserve your future and search for options. There are multiple system options, which may be payer-designed, facility-designed, or physician-designed. Close your eyes and make a guess; of those three options, which avenue is most likely to design an optimal system that treats our colleagues and our patients in the most equitable manner? The options presented above will in all likelihood evolve with both the final rulemaking and system adaptation. Hopefully, the ACS-Brandeis model is the first of many that will be developed in the procedural arena. Although I am skeptical that many anesthesia practices will benefit, please note that the proposed rules provide for an exclusion with a neutral score (0%) update if you have less than $90,000 in *allowable* charges or less than 200 patients that are enrolled in *regular* Medicare; Medicare Advantage does not count in this deliberation. However, even if you qualify, I would encourage you to assess some of the options above; the market and your future are moving in that direction!

I would like to acknowledge briefing materials contained in the publication A Guide to Physician-Focused Alternative Payment Models* jointly produced by the AMA and the Center for Healthcare Quality and Payment Reform that provided the generous excerpts, direction and resources for this article. In particular, I would like to thank Sandra Marks (AMA) and Harold Miller (CHQPR) for their copyright permission in general and allowed use of generous excerpts and edits in particular. For a deeper understanding on how you can take control of your future, this excellent resource may be accessed at:
http://www.chqpr.org/downloads/Physician-FocusedAlternativePaymentModels.pdf

Asa C. Lockhart, MD, MBA
903-521-6728
aclhart@goldencaduceusconsultants.com

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Anaphylaxis, Allergy, and Adverse Drug Reactions: Perioperative Considerations for Anesthesiologists

Jerrold H Levy, MD, FAHA, FCCM Durham, North Carolina

INTRODUCTION

Surgical patients receive multiple foreign substances in the perioperative period including drugs, blood products, or environmental antigens such as latex. Because any substance can produce an allergic or adverse reaction, clinicians must be ready to manage patients in this perioperative environment. The most life-threatening form of an allergic reaction is anaphylaxis, however, the clinical presentation of anaphylaxis may represent different immune and nonimmune responses.[1] There is confusion in the literature about the term anaphylaxis, and multiple terms have been reported to describe this reaction. In recent years, anaphylaxis has been redefined as a severe, life-threatening, generalized or systemic hypersensitivity reaction, mainly mediated by immunoglobulin E (IgE) antibodies.[2] Further, anaphylaxis represents a life-threatening allergic reaction that is rapid in onset and is associated with a significant risk for mortality.[3-6] The term *anaphylactoid*, often used to describe for non IgE-mediated reactions, is confusing and probably should no longer be used. For the practicing clinician, anaphylaxis is best defined as a clinical syndrome characterized by acute cardiopulmonary collapse following antigen (also called allergen) exposure. Much of the confusion about anaphylaxis in the literature is because many older anesthetic agents (e.g., d-tubocurarine) could directly degranulate mast cells. The incidence of immune-mediated anaphylaxis during anesthesia ranges from 1 in 10,000 to 1 in 20,000 based on mostly European reports.[7] This presentation will define the spectrum of life threatening anaphylactic and allergic reactions an anesthesiologist may encounter.

ADVERSE DRUG REACTIONS

Adverse drug reactions (ADRs) are common in hospitalized patients. Reports suggest the overall incidence of serious ADRs was 6.7% and of fatal ADRs was 0.32% from data evaluating 39 prospective studies from US hospitals.[8,9] A recent study noted fatal adverse drug reactions account for nearly 3% of all deaths in the general population, and noted hemorrhage is responsible for ~2/3 of the fatal adverse drug reactions and antithrombotic agents are involved in more than half of the suspected fatal adverse drug reactions.[10] Most serious predictable adverse drug reactions are in fact not allergic mediated events and related to other causes that include the amount of drug in the body (overdosage), unintended administration route, or known side effects (i.e., opioid-related nausea). However, some drugs have direct effects on inflammatory cells (i.e., heparin, histamine releasing agents). Unfortunately, patients often refer to any adverse drug effects as being allergic in nature. Anesthetic drugs can also produce hypotension via different mechanisms (e.g., propofol induced vasodilation) complicating the diagnosis of perioperative adverse drug reactions. Allergic drug reactions are often differentiated from other adverse drugs reactions because they are unpredictable and dose-independent (i.e., reactions due to latex allergy from latex gloves).

ALLERGY AND ANAPHYLAXIS

Allergic reactions and anaphylaxis have the same pathophysiologic mechanisms, as both are immune mediated and due to previous exposure to the antigen or a substance of similar structure. Richet and Portier first used the word anaphylaxis (ana -against, prophylaxis - protection) to describe the marked shock and resulting death that sometimes occurred in dogs immediately following a second challenge with a foreign antigen.[11] The term “allergy” was introduced in 1906 but is now often used to describe IgE-mediated allergic disease.[6] The basis of acute allergic reactions including anaphylaxis is the release of inflammatory mediators released by mast cells and basophils when an allergen interacts with membrane-bound IgE.[5,6]

PATHOPHYSIOLOGY

Anaphylaxis and allergy result from the release of multiple inflammatory mediators including membrane-derived lipids, cytokines, and chemokines.[12] When the offending antigen and IgE bind on the surface of mast cells and basophils, preformed storage granules are released that contain histamine and tryptase.[13] Other membrane derived lipid mediators are released including leukotrienes, prostaglandins, and other factors.[13] These inflammatory substances have a critical role in producing acute cardiopulmonary dysfunction, characterized by a symptom complex of bronchospasm and upper airway edema in the respiratory system, vasodilation, and increased capillary

permeability in the cardiovascular system, and urticaria in the cutaneous system.[14-16] Cardiovascular collapse during anaphylaxis results from the effects of multiple mediators on the heart and vasculature.[17] The vasodilation seen clinically can result from a spectrum of different mediators that interact with vascular endothelium and/or vascular smooth muscle.[1,18] Why some individuals develop severe cardiopulmonary dysfunction instead of minor cutaneous reactions is unknown but may relate to systemic compared to the local release of inflammatory mediators.[19] Interestingly, the original description of anaphylaxis from sea anemone toxin represents an IgG-mediated response. IgG mechanisms will be further discussed in protamine reactions that follow.

VASODILATORY SHOCK AND ANAPHYLAXIS

Vasodilatory shock occurs in anaphylaxis because of multiple mechanisms that include: excessive activation of vasodilators that increase nitric oxide synthesis to activate soluble guanylate cyclase and increase cGMP, and increased prostacyclin synthesis that activates soluble adenylate cyclase and produces cAMP. Collectively, this produces vasodilation and shock.[1,18] Nitric oxide and metabolic acidosis from shock also activate vascular potassium channels to cause persistent vasodilatation despite catecholamine therapy.[1,18] Other mediators that are released by non-IgE mechanisms may also produce shock by different mechanisms (e.g., protamine-induced acute pulmonary vasoconstriction) and heparin will be discussed in non-IgE mediated reactions.[1,18]

RECOGNITION OF ANAPHYLAXIS

Because any parenterally administered agent can cause death from anaphylaxis, anesthesiologists must diagnose and treat the acute cardiopulmonary changes that can occur. Studies from Europe suggest that perioperative drug-induced anaphylaxis may be increasing. The onset and severity of the reaction relate to the mediator's specific end organ effects. Antigenic challenge in a sensitized individual usually produces immediate clinical manifestations, but the onset may be delayed 2-20 minutes.[14,20,21] The manifestations and course of anaphylaxis are variable, ranging from minor clinical changes including urticaria to cardiopulmonary collapse including severe bronchospasm, vasodilatory shock, and pulmonary vascular injury in certain cases, leading to death. The enigma of anaphylaxis is the unpredictability of the event, the severity of the attack, and the lack of a prior allergic history. [14,20,21]

NON-IgE MEDIATED REACTIONS

Other immunologic and nonimmunologic mechanisms release inflammatory mediators independent of IgE, creating a clinical syndrome identical with anaphylaxis. Polymorphonuclear leukocyte (neutrophil) activation can occur following complement activation by immunologic (antibody mediated: IgM, IgG-antigen activation) or non-immunologic (heparin, protamine, endotoxin, cardiopulmonary bypass) pathways. [22],[23,24] Complement fragments of C3 and C5 (C3a and C5a) release histamine from mast cells and basophils, contract smooth muscle, and increase capillary permeability. Also, C5a binds receptors on neutrophils and platelets, causing chemotaxis, aggregation, and activation.[23,24] Aggregated leukocytes embolize to various organs producing microvascular occlusion and liberation of inflammatory products including oxygen-free radicals, lysosomal enzymes, and arachidonic acid metabolites (i.e. prostaglandins and leukotrienes). IgG antibodies directed against antigenic determinants or granulocyte surfaces can also activate leukocytes, and are thought to be responsible for the clinical expressions of transfusion reactions, pulmonary vasoconstriction following protamine reactions, and transfusion-related acute lung injury (TRALI).[25-27]

HEPARIN, HIT, AND KININ GENERATION

Following heparin administration, IgG antibody formation is common. These antibodies bind heparin-PF4 complexes on the platelet surface to form immune complexes that activate platelets to promote thrombin formation and thrombosis.[22] This is the clinical manifestation of heparin-induced thrombocytopenia (HIT). Nearly 7-50% of heparin-treated patients form heparin-PF4 antibodies.[22] However, recent reports of allergic reactions to heparin from China were because of an oversulfated chondroitin sulfate contaminant that directly activated the kinin-kallikrein pathway to produce bradykinin, a potent vasoactive mediator. Also, this contaminant induced generation of C3a and C5a.[28] Angiotensin converting enzyme inhibitors also may potentially increase bradykinin levels, and this is the mechanism of vasodilation, angioedema, and cough that can occur with their use.[1]

ANGIOEDEMA

Angioedema is the rapid swelling of skin, mucosa, and submucosal tissues most commonly produced by allergic reactions, but also by ACE inhibitors as noted above.[29] Oral, laryngeal, and pharyngeal swelling can occur with acute airway compromise needing urgent airway control. There are also inherited qualitative and quantitative

deficiencies of the complement C1 esterase inhibitor (C1-INH) called hereditary angioedema (HAE). Patients with HAE also have recurrent episodes of gastrointestinal manifestations of the disease. Bradykinin plays a critical role in angioedema as previously noted. Therapy of attacks includes symptomatic management and C1-INH from C1-INH concentrates. Patients with this history and documented HAE need short-term prophylaxis before surgery or dental treatment because tissue injury activates complement to increase C1-INH levels and also antifibrinolytics that inhibit plasmin mediated activation. New therapies are also being studied in this life-threatening disease. (16) A C1-INH concentrate (Cinryze™) is currently FDA-approved indicated for routine prophylaxis against angioedema attacks in adolescent and adult patients with Hereditary Angioedema (HAE).[29]

NONIMMUNOLOGIC RELEASE OF HISTAMINE

Many diverse molecular structures administered during the perioperative period degranulate mast cells to release histamine in a dose-dependent, nonimmunologic fashion.[30-33] Intravenous administration of morphine, atracurium, or vancomycin can release histamine, producing vasodilation and urticaria along the vein of administration. Although the cardiovascular effects of histamine release can be treated effectively with intravascular volume administration and/or catecholamines, the responses in different individuals may vary.[1] The newer neuromuscular blocking agents (e.g., rocuronium and cisatracurium) lack histamine releasing effects but can produce direct vasodilation and false-positive cutaneous responses that can confuse allergy testing and interpretation.[31,34] The mechanisms involved in nonimmunologic histamine release represent degranulation of mast cells but not basophils by cellular activation and stimulation of phospholipase activity in mast cells.[35]

TREATMENT PLAN

Most anesthetic drugs and agents administered perioperatively have been reported to produce anaphylaxis.[1] Therefore, a plan for treating anaphylactic reactions must be established before the event.[1] Airway maintenance, 100% oxygen administration, intravascular volume expansion, and epinephrine are essential to treat the hypotension and hypoxia that results from vasodilation, increased capillary permeability, and bronchospasm.[1] A protocol for management of anaphylaxis during general anesthesia should be considered by all clinicians. The standard considerations of cardiopulmonary resuscitation with vasoactive therapy should be followed. Therapy must be titrated to needed effects with careful monitoring. The route of administration of epinephrine and the dose depends on the patient's condition. Rapid and timely intervention with common sense must be used to treat anaphylaxis effectively. Management considerations are as follows:

Initial Therapy: Although it may not be possible to stop the administration of antigen, limiting antigen administration may prevent further mast cell and basophil activation.

Maintain Airway and Administer 100% Oxygen: Profound ventilation–perfusion abnormalities producing hypoxemia can occur with anaphylactic reactions. Administer 100% oxygen with ventilatory support as needed including treating bronchospasms if it occurs.

Discontinue Anesthetic Drugs: Inhalational anesthetic drugs are not the bronchodilators of choice in treating bronchospasm after anaphylaxis, especially during hypotension. These drugs interfere with the body's compensatory response to cardiovascular collapse, and direct acting bronchodilators should be administered if needed.

Volume Expansion: Hypovolemia rapidly follows during anaphylactic shock with up to 40% loss of intravascular fluid into the interstitial space during reactions. Therefore, volume expansion is important along with epinephrine in correcting the acute hypotension. Initially, 25 to 50 mL/kg of crystalloid or colloid solution, should be administered, with an additional 25 to 50 mL/kg may be necessary if hypotension persists.

Administer Epinephrine: Epinephrine is the drug of choice when resuscitating patients during anaphylactic shock. The α-adrenergic effects vasoconstrict to reverse hypotension; β_2 receptor stimulation bronchodilates and inhibits mediator release. The route of epinephrine administration and the dose depend on the patient's condition. Rapid and timely intervention is important when treating anaphylaxis. Of note is that patients under general anesthesia may have altered sympathoadrenergic responses to acute anaphylactic shock, whereas the patient under spinal or epidural anesthesia may be partially sympathectomized and may need even larger doses of catecholamines. In hypotensive patients, 5- to 10-μg boluses of epinephrine should be administered intravenously and incrementally titrated to restore blood pressure. (This dose of epinephrine can be obtained with 0.05 to 0.1 mL of a 1:10,000 dilution

[100 μg/mL]. Additional volume and incrementally increased doses of epinephrine should be administered until hypotension is corrected. Although infusion is an ideal method of administering epinephrine, it is usually impossible to infuse the drug through peripheral intravenous access lines during acute volume resuscitation. With cardiovascular collapse, Advanced Cardiopulmonary Life Support (ACLS) protocols should be following with full cardiopulmonary resuscitative support. Epinephrine should not be administered intravenously to patients with normal blood pressures.

Secondary Treatment

Antihistamines. Because H_1 receptors mediate many adverse effects of histamine, the intravenous administration of 0.5 to 1 mg/kg of an H_1 antagonist such as diphenhydramine may be useful in treating acute anaphylaxis. Antihistamines do not inhibit anaphylactic reactions or histamine release but compete with histamine at receptor sites. H_1 antagonists are indicated in all forms of anaphylaxis but should be given slowly to prevent precipitous hypotension in potentially hypovolemic patients.[1] The indications for administering an H_2 antagonist once anaphylaxis has occurred remain unclear.

Catecholamines. Epinephrine infusions may be useful in patients with persistent hypotension or bronchospasm after initial resuscitation.[1] Epinephrine infusions should be started at 0.05 to 0.1 μg/kg/min (5 to 10 μg/min) and titrated to correct hypotension. Norepinephrine infusions may be needed in patients with refractory hypotension due to decreased systemic vascular resistance. It may be started at 0.05 to 0.1 μg/kg/min (5 to 10 μg/min) and adjusted to correct hypotension[51].

Bronchodilators. Inhaled ß-adrenergic agents including inhaled albuterol or terbutaline if bronchospasm is a major feature[54]. Inhaled ipratropium may be especially useful for the treatment of bronchospasm in patients receiving ß-adrenergic blockers[54]. Special adaptors allow administration of bronchodilators through the endotracheal tube.

Corticosteroids. Corticosteroids have multiple antiinflammatory effects mediated by different mechanisms, including altering the activation and migration of other inflammatory cells (i.e., PMNs) after an acute reaction. They should be administered as adjuncts to resuscitative therapy when refractory bronchospasm or refractory shock occurs. The exact corticosteroid dose and choice of methylprednisone versus hydrocortisone are unclear, starting doses include 0.25 to 1 g of hydrocortisone or equivalent doses of methylprednisone. Corticosteroids may also be important in attenuating the late-phase reactions reported to occur 12 to 24 hours after anaphylaxis.

Airway Evaluation. **T**he airway should be evaluated before extubation of the trachea because of the potential for laryngeal edema. Persistent facial edema suggests airway edema. The trachea of these patients should remain intubated until the edema subsides. Developing a significant air leak after endotracheal tube cuff deflation and before extubation of the trachea is useful in assessing airway patency.

Refractory Hypotension. Reactions may be protracted with persistent hypotension, pulmonary hypertension and right ventricular dysfunction, that persist 5 to 32 hours despite resuscitation. During general anesthesia patients may have altered sympathoadrenergic responses to acute anaphylactic shock. Additional hemodynamic monitoring may be needed when hypotension persists despite therapeutic interventions as listed. Following anaphylaxis, patients should be carefully monitored for 24 hours as they may develop recurrence of manifestations following successful treatment and covered with corticosteroids for the acute event.[1]

After the initial resuscitation, norepinephrine is also an effective agent that should be considered for treating shock and dopamine should be avoided.[36] Based on the efficacy of vasopressin in reversing vasodilatory shock, it should also be considered in the therapy of anaphylactic shock not responding to therapy.[1,18,37] There are increasing laboratory and clinical reports supporting the use of vasopressin in anaphylactic shock.[38,39] When available, the use of transesophageal echocardiography in an intubated patient, or potentially transthoracic echocardiography can be useful in diagnosing the cause of acute or persistent cardiovascular dysfunction.[1] For the patient with undetectable blood pressure or following a cardiac arrest, full ACLS protocol and resuscitation must be utilized.

PRETREATMENT FOR ALLERGIC REACTIONS

Hypersensitivity reactions are more likely to occur in patients with a history of allergy, atopy, or asthma. However, this does not make it mandatory to pretreat these patients with antihistamines and/or corticosteroid because there is no data in the literature to suggest that pretreatment is effective for true anaphylactic reactions. Most of the literature on pretreatment is from studies evaluating patients with previous radiocontrast media reactions that are non-immunologic mechanisms. Although attempts to pretreat patients for anaphylaxis to latex have been used, there is no data to support this as an effective preventative measure and removal of latex from the perioperative environment is important. In fact, pretreatment may lull physicians into a false sense of security. Further, even when large doses of corticosteroids have been administered, life-threatening anaphylactic reactions have occurred.[40] Allergists have used immunospecific pretreatment therapies, but these are not practical for perioperative use.

MANAGEMENT OF THE ALLERGIC PATIENT

Patients presenting with an allergic history need to be carefully evaluated. Patients may report allergy when the reaction was a predictable adverse drug reaction. However, for practical and medico-legal purposes, that class of drug should be avoided if possible when the history is consistent with an allergic reaction, and preservative free alternatives should be chosen. The problem occurs whenever multiple drugs are simultaneously administered or when patients present with muscle relaxant reactions because of the risk of cross-reactivity to the biquarternary ammonium ions in the molecule. In this situation, skin testing may be required to see what the patient is can safely be administered.

EPIDEMIOLOGY OF ANAPHYLAXIS: AGENTS IMPLICATED

Although any molecule can produce anaphylaxis, the drugs typically associated with producing perioperative anaphylaxis include antibiotics, blood products, neuromuscular blocking drugs (NMBDs), polypeptides (aprotinin, latex, and protamine), and intravascular volume expanders.[1] During surgery, the risk of anaphylaxis varies between countries from 1/1250 to 1/18,600 per procedure with a mortality rate of 4% and an additional 2% surviving with severe brain damage.[1,7,41] NMBAs are less frequently reported in the US.

Mertes reported an 789 reactions from 1999-2001 diagnosed by clinical history, skin tests, and/or specific IgE in 518 cases (66%) and nonimmune reactions in 271 cases (34%).[42] The most common causes were NMBAs (58.2%), latex (16.7%), and antibiotics (15.1%), of which rocuronium (43%) and succinylcholine (22.6%) were the most common NMBAs reported. The positive predictive value of tryptase for the diagnosis of anaphylaxis in their study was 92.6%; the negative predictive value was 54.3%.[42] In the most recent retrospective report from France from 2011-2012, , Tacquard report NMBAs 60.6% (n=302), antibiotics 18.2% (n=91), cephalosporin 10% (n= 49), dyes 5.4% (n= 27), latex 5.2% (n=26), hypnotics 2.2% (n=11), and opioids 1.4% (n=7).[43]

LATEX ALLERGY

Latex represents an environmental agent often associated as a cause of perioperative anaphylaxis. Health care workers, children with spina bifida and urogenital abnormalities, and certain food allergies have also been recognized as individuals at increased risk for anaphylaxis to latex.[44-46] Brown reported a 24% incidence of irritant or contact dermatitis and a 12.5% incidence of latex-specific IgE positivity in Anesthesiologists.[47] Of this group, 10% were clinically asymptomatic although IgE positive. A history of atopy was also a significant risk factor for latex sensitization. Brown suggests these individuals are in their early stages of sensitization and perhaps, by avoiding latex exposure, their progression to symptomatic disease can be prevented.[47]

Patients allergic to both tropical fruits (e.g., bananas, avocados, and kiwis) and stone fruits have also been reported to have antibodies that cross-react with latex.[46,48] Multiple attempts have been made over the years to reduce latex exposure to both healthcare workers and patients. If latex allergy occurs, then strict avoidance of latex from gloves and other sources needs to be considered, following recommendations as reported.[46] Latex, however, is such a widespread environmental antigen, and patients often have concerns regarding this potential exposure.

NEUROMUSCULAR BLOCKING AGENTS

Neuromuscular blocking agents (NMBAs) have several unique molecular features that make them potential allergens. All neuromuscular blocking drugs are functionally divalent and are thus capable of cross-linking cell-

surface IgE and causing mediator release from mast cells and basophils without binding or haptenizing to larger carrier molecules. [1] NMBAs have also been implicated in epidemiological studies of anesthetic drug-induced anaphylaxis. Epidemiological data from France suggest that NMBAs are responsible for 62–81% of reactions, depending on the time period evaluated.[42,49] Rocuronium is the NMBA most reported from France. We and others have reported previously that aminosteroidal compounds as well as benzylisoquinoline-derived agents produce positive weal and flare responses when injected intradermally.[31,50,51] Estimates of anaphylactic reactions in anesthesia vary, but data suggests that false-positive skin tests may overestimate the incidence of rocuronium-induced anaphylactic reactions. [31,50,51] The differences noted in the incidence of reactions may reflect the potential for false-positive weal and flare responses. [31,50,51] NMBAs can also produce direct vasodilation by multiple mechanisms, which include calcium channel blockade. The false-positive skin tests that were reported to be biopsy-negative for mast cell degranulation clearly confound interpreting skin tests in patients who have had life-threatening cardiopulmonary collapse. Dilute solutions of NMBAs need to be used when skin testing for potential allergic reactions to these agents. However, the exact concentration that should be used is unclear. Since skin-testing procedures are important in evaluating potential drug allergies, the threshold for direct vasodilating and false-positive effects must be determined whenever subjects are skin-tested for a particular drug.

POLYPEPTIDES AND BLOOD PRODUCTS

Polypeptides are larger molecular weight molecules that pose greater potential to be antigenic, and include aprotinin, latex, and protamine. Diabetic patients receiving protamine containing insulin as neutral protamine Hagedorn (NPH) or protamine insulin have a 10-30 fold increased risk for anaphylactic reactions to protamine when used for heparin reversal, with a risk of 0.6-2% in this patient population.[40,52] Because protamine is often given with blood products, protamine is often implicated as the causative agent in adverse reactions, especially in cardiac surgical patients. Platelet and other allogeneic blood transfusions can produce a series of adverse reactions by multiple mechanisms, and blood products have a greater potential for allergic reactions including TRALI.[25] Although antigen avoidance is one of the most important considerations in preventing anaphylaxis, this is not always possible, especially with certain agents where alternatives are not available. Protamine is an important example of where alternatives are under investigation, but not currently available.

EVALUATING THE PATIENT FOLLOWING ANAPHYLAXIS

A detailed history is one of the most important considerations to evaluate a patient following anaphylaxis, determining what agents were administered, and what the temporal sequence was.[53] Also, after resuscitation collect a red top tube (serum) for mast cell tryptase, preferably within 1-2 hours of the reaction, and then repeat 24 hours later. Serum can also be collected postmortem, which may be important for you medico-legally. Most hospital laboratories will need to send this test to a reference laboratory. If tryptase is positive, sending the patient for an allergy consultation may be useful if the temporal sequence is confusing, and the agent responsible needs further investigation. Often, a positive mast cell tryptase usually represents an IgE-mediated reaction (i.e., anaphylaxis) but vancomycin and other histamine releasers can also increase tryptase.[35] Negative mast cell tryptase tests are rarely associated with positive skin tests and antibody tests. IgG reactions due to protamine, or blood products are unlikely to increase tryptase. Few laboratory based tests are available for determining immunologic testing, so skin testing is required if better differentiation of the agent responsible is required.

CONCLUSIONS

Anaphylaxis represents an important potential problem and an important cause of life-threatening events. Clinicians must be able to recognize and treat these life-threatening events if they occur. Clinicians should remember that test doses may produce anaphylaxis. There are few in vitro tests available to assess patients at high risk for reexposure anaphylaxis. Anaphylactic reactions represent a continuing challenge, but rapid diagnosis and treatment are important in preventing adverse clinical outcomes.

SUGGESTED WEB SITES: AnaphylaxisWeb.com, FDA.gov

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Clinical Pathways for Total Joint Arthroplasty: Essential Components for Success

James R. Hebl, M.D. **Rochester, MN**

Clinical Pathways: An Overview

The term *clinical pathway* refers to a multidisciplinary process of mutual decision-making that results in the organized care of a well-defined group of patients during a well-defined period of time.[1, 2] Clinical pathways were first introduced in the 1980's when escalating medical costs pressured physicians to decrease resource utilization without jeopardizing patient safety or clinical outcomes. At that time, pathways were typically procedure-specific (e.g., coronary artery bypass grafting, total knee arthroplasty) and tailored to a specific institution.[3, 4] As a result, tremendous variability often existed from one institutional clinical pathway to another, making clinical comparisons between pathways and formal scientific study exceedingly difficult.

Despite this variability, it is generally agreed upon that clinical pathways provide several distinct advantages. These include the ability to (1) provide coordinated care between departments and across patient care units; (2) standardize patient care and reduce hospital length-of-stay; (3) convert typical inpatient (i.e., same-day admission) procedures to outpatient (i.e., same-day discharge) procedures; (4) prompt change in the care process to better emphasize patient outcomes and cost containment; (5) control hospital costs; and (6) serve as a marketing tool with the public or with third-party payers.[5]

Despite these challenges, this review will summarize the important components of a successful clinical pathway and attempt to evaluate the impact of differing clinical pathways on major perioperative outcomes after total joint arthroplasty. Perioperative outcomes that will be evaluated include postoperative complications, hospital length-of stay, clinical outcomes, and medical costs.

Clinical Pathway Components

Effective clinical pathways for major orthopedic surgery include the coordination and standardization of several patient care activities during the pre-, intra-, and postoperative period. Essential components of some of the most effective orthopedic clinical pathways are listed in Table 1.

Preoperative Patient Education

Major orthopedic surgery can be a stressful and anxiety-provoking experience for most patients. Bondy and colleagues [6] examined the effect of anesthesia patient education on preoperative anxiety and found that a detailed patient education program may have several beneficial effects. Preoperative patient education may significantly relieve patient anxiety and emotional stress by providing a better understanding of the perioperative process (e.g., preoperative evaluation, hospital admission process, anesthetic options, expected clinical course) and establishing clear expectations with regard to hospital length-of-stay and the discharge process (e.g., dismissal to home vs. rehabilitation swing-bed vs. nursing home). Because patients have a better understanding of the perioperative process, they will often present for surgery with increased confidence in the therapeutic plan and a willingness to more actively participate in their care. Increased participation often results in greater patient satisfaction and potentially improved perioperative outcomes. However, the extent to which patient education influences postoperative outcomes is somewhat unclear.[7-9] McDonald and colleagues [8] demonstrated that preoperative patient education may result in a modest benefit in preoperative anxiety. However, this benefit failed to persist on Postoperative Day (POD) 2 or at the time of hospital discharge. A review of the Cochrane Database on this topic fails to demonstrate that

preoperative patient education has a significant impact on postoperative clinical outcomes (e.g., postoperative pain, functional outcomes, hospital length-of-stay) in patients undergoing total hip or total knee arthroplasty.

Table 1. Essential Clinical Pathway Components

Preoperative
- Preoperative patient education program
- Appropriate management of preoperative pain and psychological symptoms (fear, anxiety, depression)

Intraoperative
- Development of a comprehensive multimodal analgesic regimen
- The use of peripheral nerve blockade and continuous perineural catheters
- Postanesthesia Care Unit (PACU) algorithms for the management of acute postoperative pain

Postoperative
- Standardized method of pain assessment on the nursing floors and pain score documentation within the medical record
- Early and accelerated rehabilitation regimen
- Development of an integrated and multidisciplinary Acute Pain Service
- Staff education regarding the importance of pain management
- Written protocols for acute postoperative pain management

Multimodal Analgesia

Patients undergoing total knee and total hip arthroplasty experience significant postoperative pain.[10] Severe pain occurs in 60% of patients and moderate pain in up to 30% of patients undergoing total knee arthroplasty. Failure to provide adequate analgesia may impede early physical therapy and rapid rehabilitation,[11] which are both important factors for maintaining joint range of motion and facilitating hospital discharge.[12] In an effort to avoid many of the side effects commonly associated with opioid-induced analgesia, clinicians have begun adopting multimodal therapeutic regimens. Multimodal analgesia has become an important concept in the field of modern pain management.[12-17] The concept is designed to combat pain perception along several pathways of signal transmission, including the surgical site and surrounding tissues, local sensory nerves, and central nervous system. Advantages include superior analgesia secondary to the synergistic effects of multiple agents acting via different pathways, the ability to limit parenteral opioid administration, and minimizing opioid-related side effects. Several investigations have demonstrated the beneficial effects of multimodal analgesia,[14-16] including its value in patients undergoing major orthopedic joint replacement surgery.[17-24]

Several medications may be used as part of a multimodal analgesic pathway. Specifically, the use of acetaminophen,[25] non-steroidal anti-inflammatory agents,[26] selective cyclooxygenase-2 inhibitors,[18] pregabalin,[21] and ketamine,[22] have all been shown to have analgesic benefits in patients undergoing joint replacement surgery. Most experts recommend using multiple agents during the pre- and postoperative period in small quantitative doses to maximize the analgesic effect while minimizing associated side effects. Documented benefits include superior postoperative analgesia,[18, 22, 25, 26] reduced supplemental opioid requirements, [18, 21, 22, 25, 26] fewer opioid-related side effects,[13, 18] improved joint range-of-motion,[18, 21] fewer postoperative sleep disturbances,[18] shorter time to achieve

hospital discharge criteria,[21] improved functional mobility,[22] and a lower incidence of chronic neuropathic pain.[21]

Finally, poorly controlled acute postoperative (i.e., nociceptive) pain may contribute to the development of chronic neuropathic pain or complex regional pain syndrome after total joint arthroplasty.[27] Nikolajsen and colleagues examined the Danish Hip Arthroplasty Registry and found that 12% of patients continue to experience moderate-to-severe pain 12-18 months after surgery.[28] Similarly, up to 13% of total knee arthroplasty patients may experience moderate-to-severe pain 12-months after surgery.[29] Additional risk factors for the development of chronic postoperative pain include *preoperative* pain for greater than 1-month, an increased intensity of preoperative pain, and a patient history of preoperative fear, anxiety or depression.[29, 30] Poorly controlled postoperative pain has also been shown to impede global recovery and lower the reported quality of life 6-months after surgery.[31] Therefore, clinical pathways that integrate (1) a comprehensive multimodal analgesic regimen to adequately manage pre- *and* postoperative pain; and (2) a comprehensive psychiatric program to manage preoperative psychological symptoms may have a significant benefit in improving long-term clinical and psychiatric outcomes.

Peripheral Nerve Blockade and Continuous Perineural Catheters

Many treatment regimens for managing severe postoperative orthopedic pain include significant doses of parenteral opioids. These treatment regimens are commonly associated with significant opioid-related side effects such as sedation, nausea, vomiting, ileus, and urinary retention that can adversely effect patient outcomes and prolong hospital length-of-stay.[19] Therefore, clinical pathways that minimize (or eliminate) opioid administration may significantly reduce opioid-related side effects and improve postoperative patient outcomes.

The integration of regional anesthesia and peripheral nerve blockade into clinical pathways for orthopedic surgery is an essential step to minimize opioid use and improve perioperative outcomes. Both single-injection [32-35] and continuous [36-40] peripheral nerve block techniques have been shown to provide superior analgesia, reduce supplemental opioid requirements, decrease opioid-related side effects, and improve functional outcomes after total joint arthroplasty. In a recent meta-analysis of 19 articles and 603 patients, Richman and colleagues [41] also demonstrated that patients receiving continuous peripheral nerve blockade have superior analgesia, fewer opioid-related side effects (nausea, vomiting, pruritus, sedation), and improved patient satisfaction when compared to traditional intravenous opioids alone. Although single-injection techniques have been shown to be superior to placebo or systemic analgesia [32-35], comparison studies have shown that single-injection blocks fail to provide the extended benefits of continuous perineural catheters.[37, 42, 43] Continuous peripheral nerve block techniques have also been shown to have similar analgesia – but a more desirable side effect profile – when compared to epidural analgesia.[44] A recent review by Fowler and colleagues [44] demonstrated that patients receiving peripheral nerve blocks had less urinary retention and fewer episodes of postoperative hypotension when compared to patients receiving neuraxial techniques.

A primary concern regarding the use of peripheral nerve blockade is the risk of neurologic complications. Barrington and colleagues [45] recently performed a prospective audit of more than 7,000 peripheral nerve blocks performed at 9 Australian hospitals. Overall, they identified a neurologic injury rate of 0.5%. However, only 10% of these injuries were attributed to peripheral nerve blockade suggesting that the vast majority of perioperative nerve injuries have a non-anesthesia related etiology. The nerve injury rate attributed to peripheral nerve blockade was found to be 0.04% – a rate similar to other large-scale investigations.[46, 47] Jacob and colleagues [48] have also demonstrated that neither the type of intraoperative anesthesia (general versus neuraxial) nor the use of peripheral nerve blockade was associated

with an increased risk of perioperative nerve injury in 12,329 patients undergoing total knee arthroplasty. Rather, bilateral surgical procedures and total tourniquet time were found to be associated with an increased risk of nerve injury.[48]

Standardized Pain Assessment and Documentation, Pain Management Protocols and Staff Education

In 2001, the Joint Commission declared pain as the "Fifth Vital Sign" and instituted *Pain Management Standards* for accredited ambulatory care facilities, behavioral health care organizations, critical access hospitals, home care providers, hospitals, office-based surgery practices, and long-term care providers.[49] The standard requires health care providers to (1) Appropriately assess and manage pain; (2) Document pain management interventions and subsequent reassessments; (3) Perform pain screenings during initial patient assessments; and (4) Educate patients and their families about pain management. Benhamou [50] and Fletcher [51] report that similar guidelines and recommendations have been put forward by the Royal College of Surgeons, the French Ministry of Health, the French Society of Anesthesia and Intensive Care, the European Task Force on Pain Management, and the International Association for the Study of Pain. The overwhelming consensus is that each of these interventions should be considered essential components to any clinical pathway designed to optimize pain management and patient care. Despite these recommendations, the literature suggests that pain remains under-treated in both U.S. [52] and European [53] health care facilities – in part, because of a lack of adherence to previously published standards and guidelines.

Early and Accelerated Rehabilitation

An early and accelerated rehabilitation program should also be integrated into clinical pathways designed for total hip and total knee arthroplasty patients. A review of the literature suggests that early and accelerated rehabilitation may have a major impact on improved perioperative outcomes in orthopedic patients.[9, 55] Munin and colleagues [55] demonstrated that early inpatient rehabilitation resulted in a shorter hospital length-of-stay and a more rapid attainment of short-term functional outcomes after joint replacement surgery when compared to a delayed rehabilitation program. Pour and colleagues [9] also examined the impact of an accelerated pre- and postoperative rehabilitation program versus a standard regimen on functional outcomes after total hip arthroplasty. Patients randomized to the accelerated pathway were seen earlier on the day of surgery and more frequently on subsequent postoperative days (twice daily versus once daily). There was also a greater emphasis on oral analgesics (versus intravenous patient-controlled analgesia) in patients receiving accelerated rehabilitation. In addition to a shorter hospital length-of-stay, accelerated pathway patients were able to walk for longer distances, had improved pain control, and reported higher patient satisfaction at the time of hospital discharge.[9]

Finally, Mahomed and colleagues [56] have demonstrated that rehabilitation after total hip or total knee arthroplasty does not need to be restricted to the inpatient setting. Home-based rehabilitation programs may provide similar degrees of postoperative analgesia, functional outcomes, and patient satisfaction at a significantly lower cost when compared to hospital-based regimens.[56]

Clinical Pathways and Perioperative Outcomes

The goal of most clinical pathways is to provide standardized, evidence-based care to patients in such a way as to minimize the variability of care provided by individual providers. This process has the potential to significantly enhance the quality, improve the safety, and reduce the cost associated with surgical procedures. Several clinical pathways have been reported in the literature for patients undergoing total joint arthroplasty [1, 4, 19, 20, 57-59]; with no two pathways being identical. As a result, comparison of clinical pathways is exceedingly difficult – forcing systematic reviews or meta-analyses that examine the topic to comment on the "concept" of clinical pathways versus their individual component parts. Barbieri and

colleagues [1] recently performed a systematic review of clinical pathways used for joint replacement surgery. The review examined 22 studies and included 6,316 patients. The aggregate results demonstrated a significant reduction in postoperative complications (deep venous thrombosis, pulmonary embolism, manipulation, superficial infection, deep infection, heel decubitus ulcers), a shorter hospital length-of-stay, and lower hospital costs in patients undergoing clinical pathways versus standard care.[1] Publications from the University of California – Irvine, the University of Utah, and the Mayo Clinic are described below; and represent typical examples of clinical pathways developed for orthopedic surgical patients.

Clinical Pathways for Total Joint Arthroplasty

Skinner and colleagues [57] performed a retrospective, case-controlled investigation of 102 patients undergoing total hip or total knee arthroplasty at the University of California – Irvine. They compared a multimodal clinical pathway that incorporated COX-II inhibitors, tramadol, dexamethasone, acetaminophen, and intra-articular bupivacaine to patients receiving "standard management" with patient-controlled analgesia and intravenous opioids. Importantly, the authors did *not* incorporate regional anesthesia or peripheral nerve blockade as a component of the clinical pathway. Clinical endpoints were evaluated during POD 1 through 4. For patients receiving the clinical pathway, opioid requirements were reduced 66% for total hip arthroplasty (POD 2 only) and 68% for total knee arthroplasty (POD 3 only). Although VAS pain scores were no different among total hip arthroplasty patients, patients undergoing total knee arthroplasty reported lower VAS pain scores on POD 2 and at the time of hospital discharge. Implementation of the clinical pathway resulted in no differences in perioperative complications. Hospital length-of-stay was reduced in only total knee arthroplasty patients undergoing the clinical pathway (4.0 vs. 4.9 days; $P<0.02$). [57]

In contrast to clinical pathways *not* incorporating regional anesthesia [57] – multimodal regimens utilizing peripheral nerve blockade have been shown to consistently reduce hospital length-of-stay, improve perioperative analgesia with fewer opioid medications, facilitate postoperative rehabilitation, and reduce opioid-related side effects.[19, 20, 58] Peters and colleagues [58] performed a retrospective analysis of 100 patients undergoing total hip and total knee arthroplasty at the University of Utah.[58] The clinical pathway included a multimodal analgesic regimen (sustained-release oxycodone, COX-II inhibitors, and acetaminophen), intraoperative regional anesthesia with intrathecal opioids, and an ultrasound-guided femoral nerve catheter (total knee arthroplasty patients only) for extended postoperative analgesia. Prior to wound closure, patients undergoing both total hip and total knee arthroplasty received <1 mg/kg of 0.25% bupivacaine injected into the deep and subcutaneous tissues by the orthopedic surgeon. A multimodal oral analgesic regimen was then continued into the postoperative period. Control patients were managed with intraoperative general or spinal anesthesia (within intrathecal morphine), continuous femoral nerve blockade (total knee arthroplasty patients only), and postoperative patient-controlled analgesia with intravenous opioids. Patients receiving the clinical pathway had significantly lower pain scores at rest on POD 1 and 2, lower opioid requirements, improved ambulation during rehabilitation sessions, and reduced hospital length-of-stay. There were no differences in perioperative complications when comparing clinical pathway to control patients. Overall, the investigators concluded that the development and implementation of a comprehensive clinical pathway combined with early and aggressive physical therapy improves perioperative outcomes, shortens hospital length-of-stay, and allows patients to achieved physical therapy goals earlier when compared to non-clinical pathway patients.[58]

Finally, Hebl and colleagues have described the development and implementation of the Mayo Clinic Total Joint Regional Anesthesia (TJRA) Clinical Pathway in patients undergoing both minimally-invasive [19] and traditional [20] total hip and total knee arthroplasty. The TJRA Clinical Pathway incorporates preoperative patient education, a multimodal analgesic regimen emphasizing peripheral nerve blockade,

standardized PACU algorithms, pain assessments, and medical record documentation, pain management protocols, and a standardized postoperative physical therapy regimen for patients undergoing total joint arthroplasty. Similar to most clinical pathways, the TJRA Clinical Pathway was developed by a multidisciplinary group of Mayo Clinic surgeons, anesthesiologists, pharmacists, nurses, and physical therapy staff based upon their collective experience and exposure to physicians and practice models outside the institution. Although the basic principles of the pathway have remained unchanged (e.g., preoperative patient education, multimodal analgesia, peripheral nerve blockade, pain management protocols), its individual components are continually being evaluated and modified as necessary based upon changes in clinical practice. The current multimodal analgesic and regional anesthesia components of the TJRA Clinical Pathway are listed in Appendix 1.

The Mayo Clinic TJRA Clinical Pathway was first used in patients undergoing minimally-invasive total hip (n=20) and total knee (n=20) arthroplasty.[19] Study patients were prospectively enrolled and compared to matched historical controls undergoing traditional surgical and anesthetic techniques. Matching criteria included the type of surgical procedure, age, gender, and American Society of Anesthesiologists physical status (ASA PS) classification. Patients undergoing minimally-invasive surgery in combination with the TJRA Clinical Pathway had significantly lower pain scores both at rest and with physical therapy, required fewer opioid medications, were able to ambulate significantly sooner, and experienced less urinary retention and postoperative cognitive dysfunction when compared to matched controls. Cognitive dysfunction was defined as disorientation to person, place, or time, hallucinations, or any other cognitive condition requiring further assessment by a physician. Based upon these criteria, approximately 15% of control patients and 1% of TJRA patients experience postoperative cognitive dysfunction during their hospitalization. Hospital length-of-stay was also significantly shorter among TJRA patients (2.8 days vs. 5.0 days; $P<0.01$).[19]

The Mayo Clinic TJRA Clinical Pathways has also been utilized in patients undergoing traditional (i.e., non-minimally invasive) total hip and total knee arthroplasty.[20] Patients undergoing joint replacement surgery with the TJRA Clinical Pathway experience superior analgesia with fewer opioid-related side-effects when compared to control patients. Verbal analog pain scores (VAS) were significantly lower among TJRA patients both at rest ($P<0.001$) and with activity ($P<0.001$) during their entire hospital stay. Opioid requirements were significantly less among TJRA patients from the pre-/intra-operative period until the beginning of Postoperative Day 2 ($P=0.04$). Opioid related side-effects such as nausea ($P<0.001$), vomiting ($P=0.01$), and urinary retention ($P<0.001$) were also significantly reduced for TJRA patients throughout most of the perioperative period. There was no significant difference in the frequency of pruritus between groups.[20]

Postoperative milestones (bed-to-chair transfer, discharge eligibility, and hospital dismissal) were achieved significantly sooner in patients receiving the multimodal TJRA protocol. The ability to transfer from bed to chair occurs a mean of 0.2 ± 0.6 days sooner among TJRA patients when compared to matched controls ($P=0.001$). However, nearly all patients were able to accomplish this milestone by the end of POD 1. Discharge eligibility was also achieved a mean of 1.7 ± 1.9 days sooner among TJRA patients when compared to matched controls ($P<0.0001$). Hospital length-of-stay was 3.8 days for TJRA patients and 5.0 days for controls ($P<0.001$). At the time of hospital dismissal, joint range-of-motion was significantly better among TJRA patients (90° vs. 85°; $P=0.008$). Importantly, the small gains in range-of-motion observed at hospital dismissal persisted at 6-8 weeks postoperatively (106° vs. 99°; $P=0.03$).[20]

Severe postoperative complications (neurologic injury, myocardial infarction, renal dysfunction, localized bleeding, deep venous thrombosis/pulmonary embolism, joint dislocation, wound infection) are similar

among TJRA patients and patients receiving patient-controlled analgesia (PCA). However, urinary retention (P<0.001) and postoperative ileus occurred significantly more often among control patients (7% vs. 1%; P=0.01) resulting in delayed postoperative feedings.[20]

Clinical Pathways and Economic Outcomes

Total hip and total knee arthroplasty are two of the most commonly performed surgical procedures in the United States and represent the single greatest Medicare procedural expenditure.[60, 61] Recent data from the United States Healthcare Cost and Utilization Project report that both the number and cost of total knee and total hip replacement surgeries have increased more than 300% during the past decade.[62, 63] Furthermore, the American Academy of Orthopaedic Surgeons and other independent population-based studies estimate that the number of total joint replacement surgeries will continue to grow.[64, 65] In fact, the number of total hip arthroplasties is expected to increase by as much as 50% per year; and the number of total knee arthroplasties by 300% per year through the year 2030.[64] Given this trend, and the fact that Medicare reimbursement continues to decline, orthopedic patients may have a major economic impact on hospitals and other health care facilities during the next 20 years.[66] Therefore, any changes in surgical or anesthetic practice that can reduce the cost associated with these procedures – while maintaining the same degree of high-quality and efficient patient care – may have a significant impact on overall United States health care expenditures.

Medical costs associated with an episode of care can be classified into three major categories (1) indirect costs; (2) intangible costs; and (3) direct costs.[67] *Indirect costs* include the cost of lost productivity related to the morbidity and mortality of the disease state. *Intangible costs* include the cost associated with pain and suffering from the disease state. *Direct costs* include medical supplies, labor, and time – and can be further divided into Medicare Part A costs and Medicare Part B costs (Figure 1). Several cohort studies have linked the use of clinical pathways with lower variable costs.[7, 68-74] Other studies have demonstrated that the development and implementation of a clinical pathway for patients undergoing total hip or total knee arthroplasty may significantly reduce both total hospital [4] and direct medical costs [62] while maintaining or improving perioperative outcomes.

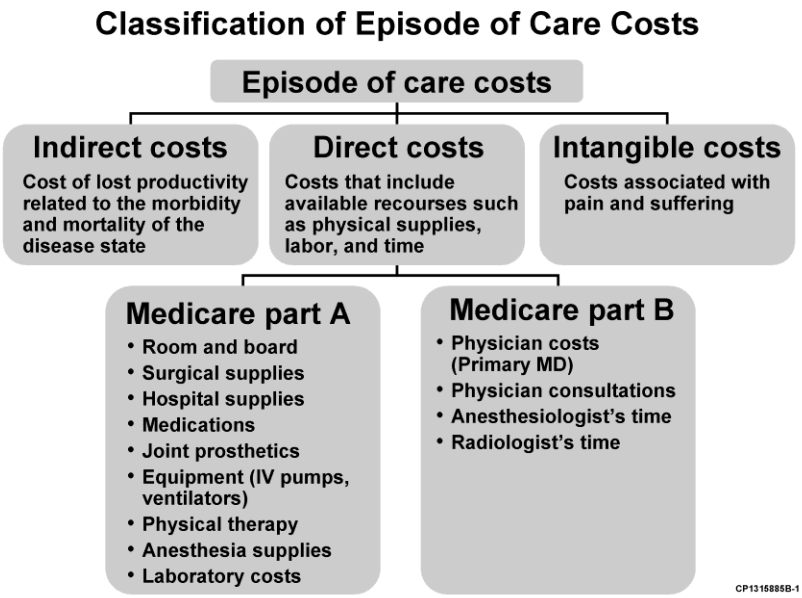

Figure 1. Classification of Episode of Care Costs.

A reduction in hospital length-of-stay is often considered a cost-saving benefit during the perioperative period. However, cost savings associated with reductions in hospital length-of-stay are directly related to the total duration of stay; and may not necessarily reflect a significant source of cost savings. For example, although hospital "room and board" costs remain constant throughout a hospitalization, treatment costs associated with a hospitalization are often greatest during the initial 48-72 hours of care (reflecting greater care demands during the patient's initial illness); with a subsequent decline in daily direct medical (i.e., treatment) costs (Figure 2).[75] Therefore, a reduction in hospital length-of-stay from 72 hours to 48 hours will result in significantly greater cost savings than a length-of-stay reduction from 7 days to 6 days. As a result, hospital administrators must understand that an isolated reduction in length-of-stay may (or may not) result in a positive financial impact for the hospital or institution.

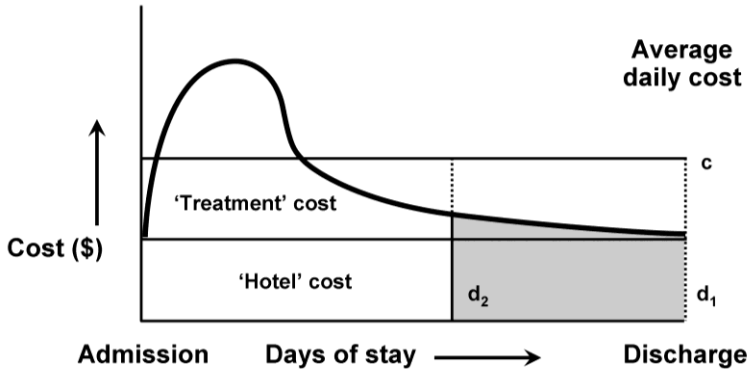

Figure 2. Estimating the cost savings associated with reductions in hospital length-of-stay. Hospital stays include a daily fixed cost called the "hotel" cost. Additionally, a "treatment" cost is added to each hospital day. During hospitalization the treatment costs are often greatest during the initial portion of the hospital stay reflecting greater care demands during the patient's initial illness (represented above). The result is that decreasing the length of stay from d_1 to d_2 at the end of hospitalization will likely not result in the same amount of savings as the daily average cost (line c) would estimate.

mandated that pain management become an integral component of all patient care activities as a condition of hospital accreditation. As a result, many institutions implemented aggressive pain management protocols that were guided by patient reports of pain intensity as quantified by a numeric pain scale. Although numeric pains scales may be useful to monitor pain *trends* within a given patient, these subjective methods of pain assessment are an extremely poor guide for directed analgesic management. In fact, because these subjective and often non-reproducible pain scales do not take into consideration patient comorbidities or associated medication risks, adverse outcomes such as oversedation and respiratory depression may lead to catastrophic outcomes – including death.[70, 76, 77]

Vila and colleagues [78] demonstrated the potential *negative* impact of implementing a hospital-wide pain management protocol that treats pain based upon patient self-reports. After implementation of a numeric pain treatment algorithm, the number of adverse drug reactions secondary to opioid oversedation more than doubled when compared to pre-implementation values (24.5 vs. 11 adverse events per 100,000 inpatient

hospital days; P<0.001). A decreased level of consciousness preceded 94% of events, emphasizing the importance of careful clinical assessment and ongoing patient monitoring while managing pain.[78] Overmedication in preparation for an imaging study,[70] overmedication after discharge from the ICU ,[70] and the first 24 hours after surgery [77] appear to be the clinical scenarios or time periods in which patients are at greatest risk for respiratory depression and oversedation.

Finally, clinical pathways that incorporate regional anesthesia and peripheral nerve blockade may increase the likelihood of residual motor blockade – which may impede early mobilization, increase the risk of patient falls, and prolong hospital length-of-stay.[43, 79-82] Kandasami and colleagues [80] recently reported a fall rate of 2% in patients undergoing total knee arthroplasty with the use of femoral nerve blockade. Fall-related injuries included wound dehiscence (n=4) and periprosthetic fracture (n=1). Hospital length-of-stays were extended 10 to 42 days secondary to complications from the fall. However, it has been argued that residual motor blockade is a multifactorial phenomenon – and cannot be entirely attributed to regional anesthesia. In addition to local anesthetic-induced quadriceps weakness, it is believed that motor block can occur secondary to surgical pain, muscle spasm, joint stiffness, swelling, dysesthesias, or other surgical factors.[83] Regardless of the cause, anesthesia providers need to play their role in minimizing the risk of residual motor blockade in patients undergoing total hip and total knee arthroplasty. Clinical pathways that incorporate peripheral nerve blockade need to do so in such a way that the benefits of regional anesthesia are achieved (i.e., identifying the optimal local anesthetic, dose, and concentration); while the contemporary concerns of delayed rehabilitation, prolonged hospital length-of-stay, and increased hospital costs are avoided.

Summary

Total hip and total knee arthroplasty are two of the most commonly performed surgical procedures in the United States with increased volumes expected over the next several decades. Clinical pathways represent a standardized, evidence-based approach to patient care designed to enhance the quality, improve the safety, and reduce the cost associated with surgical procedures. Clinical pathways for total joint arthroplasty have been shown to significantly improve the perioperative outcomes of patients undergoing joint replacement surgery. Effective clinical pathways include preoperative patient education, a multimodal analgesic regimen, peripheral nerve blockade, standardized pain assessment and medical record documentation, pain management protocols, staff education, and early and accelerated rehabilitation. Potential clinical benefits include superior postoperative analgesia, fewer opioid-related side effects, earlier ambulation, improved joint range-of-motion, fewer postoperative complications, and reduced hospital length-of-stays. The financial benefits of clinical pathways include a reduction in both total hospital and direct medical costs. However, further study is needed to determine precisely which component(s) of a comprehensive clinical pathway are most active in contributing to these clinical and financial benefits.

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Appendix 1. Mayo Clinic Total Joint Regional Anesthesia Clinical Pathway *

Patient Waiting Area (Pre-op)

- Oxycodone controlled release (OxyContin®) 20 mg PO once on arrival to patient waiting area if patient 18-59 years old; or 10 mg PO if patient 60-74 years old.
- Acetaminophen (Tylenol®) 1000 mg PO once on arrival to patient waiting area.
- Celecoxib (Celebrex®) 400 mg PO once on arrival to patient waiting area.
- Gabapentin (Neurontin®) 600 mg PO once on arrival to patient waiting area if patient 18-59 years old; or 300 mg PO if patient 60-69 years old.

Peripheral Nerve Catheter Infusions

(1) Femoral Nerve ***or*** Adductor Canal Catheter (TKA): 20 mL (Adductor) or 30 mL (Femoral) bolus dose of Bupivacaine 0.5% + 1:200,000 epinephrine at time of placement

- Bupivacaine 0.2% 10 mL bolus upon arrival in PACU; then initiate continuous infusion Bupivacaine 0.2% at 10 mL/hour.
- Continue Bupivacaine 0.2% continuous infusion at 10 mL/hour until 0600 the day after surgery. At 0600 the day after surgery, change to Bupivacaine 0.1% continuous infusion at 10 mL/hour. On the second day after surgery, stop infusion and discontinue femoral nerve catheter infusion before 0800.

(2) Posterior Lumbar Plexus Catheter (THA): 30 mL bolus dose of Bupivacaine 0.5% + 1:200,000 epinephrine at time of placement

- Bupivacaine 0.2% 10 mL bolus upon arrival in PACU; then initiate continuous infusion Bupivacaine 0.2% at 10 mL/hour
- Continue Bupivacaine 0.2% continuous infusion at 10 mL/hour until 0600 the day after surgery. At 0600 the day after surgery, change to Bupivacaine 0.1% continuous infusion at 10 mL/hour. On the second day after surgery, stop infusion and discontinue psoas nerve catheter infusion before 0800.

Intraoperative

- Spinal anesthesia preferred intraoperative primary anesthetic
- Fentanyl 50-150 mcg IV PRN
- Ketamine 10-20 mg IV (150-200 mcg/kg; Maximum 20 mg)
- Dexamethasone 4-8 mg IV
- Tranexamic acid 1 g I.V. prior to incision and 1 g I.V. during closure

  NOTE: Tranexamic acid is not administered to high-risk ASA III or IV patients (High risk = Prior history of DVT, PE, MI, CVA CABG, Stent placement, or other Pro-thrombotic conditions)

Post-Anesthesia Care Unit (PACU)

- Oxycodone 5-10 mg PO PRN once for pain rated 4 or greater. Give 5 mg if patient 70 years old or older; give 10 mg if patient 18-69 years old.
- Fentanyl 25 mcg IV PRN for pain rated 7 or greater; may repeat every 5 minutes (maximum 100 mcg)
- Ketorolac (Toradol®) 15 mg IV PRN once for pain rated 4 or greater

Postoperative Nursing Floor †

- Acetaminophen (Tylenol®) 1000 mg PO 3 times daily at 0800, 1200, and 1600 hours.
- Tramadol (Ultram®) 50–100 mg PO every 6 hours
- Celecoxib (Celebrex®) 200 mg PO BID x 10 days
- Ketorolac (Toradol®) 15 mg IV every 6 hours PRN for pain rated more than 4 (maximum of 4 doses)

• Oxycodone 5–10 mg PO every 4 hours PRN. Give 5 mg if patient reports pain and rates pain score less than 4; give10 mg if patient complains of pain rated 4 or greater.
Monitoring • Continuous pulse oximetry telemetry monitoring for 48 hours postoperatively

* Perioperative analgesic options are selected based upon each patient's associated comorbidities.
† Selection of postoperative medications at surgeon's discretion.

ANESTHESIOLOGY 2017
BOSTON OCTOBER 21-25

Intraop Physiology: A key to delirium prevention

Miles Berger, MD PhD **Durham, NC**

This review course lecture will cover both retrospective studies that have attempted to correlate intraoperative physiologic data and/or parameters with the severity, duration of and incidence of postoperative cognitive dysfunction (POCD) and/or delirium, as well as prospective interventional trials that have determined whether specific intraoperative monitoring and/or physiologic management strategies or interventions lead to changes in the same POCD and/or delirium parameters. In particular, this lecture will cover studies that have measured the relationship between POCD/delirium and intraoperative hemodynamic, respiratory, and cerebral physiology.

Before starting these main sections of the RCL, we will first briefly review the age-dependent changes that occur in the human brain and central nervous system, since these changes are present in many of our older patients and should be kept in mind when considering intraoperative physiologic management for delirium prevention. Following this introduction, in the section on intraoperative hemodynamic management, we will first review studies that have examined correlations between mean arterial pressure, cerebral perfusion pressure and cognitive function in controlled settings outside of the operative room. After this introduction, we will then review the literature on intraoperative blood pressure control and POCD/delirium. We will also discuss the concept of cerebral autoregulation, and discuss studies that have examined cerebral autoregulation in patients anesthetized for both cardiac and non-cardiac surgery. In particular, we will review data on how the cerebral autoregulation curve shifts in patients with untreated vs treated hypertension vs in patients without hypertension, as well as the effects of age upon cerebral autoregulation . We will then discuss the implication that cerebral perfusion pressure may depend not only intraoperative mean arterial pressure, but also on the relationship between intraoperative mean arterial pressure and the patient's average mean arterial pressure during the weeks, months and years before his or her surgery. In this section of the talk, we will also discuss the mechanistic regulation of vascular pressure, and review data on whether different vasopressors may have differential effects of cerebral perfusion pressure independent of their effects on mean arterial pressure measured via a non-invasive cuff at a brachial position or from a radial arterial line. We will also review data suggesting that "alpine anesthesia" or extreme variations in intraoperative blood pressure and hemodynamic control may be associated with an increased risk of POCD and/or delirium.

This section of the talk will conclude with the idea that we need future prospective studies that move beyond simply randomizing patients to one of two different mean arterial pressure range targets in the operating room and then measuring POCD/delirium parameters, to studies that randomize patients to different targets determined on an individual patient basis relative to each patient's baseline blood pressure range.

In the section on respiratory management, we will first review the literature on oxygenation and cerebral function in controlled laboratory settings and in extreme environments. This section of the talk will include the surprising finding that healthy humans (including several anesthesiologists) performing high altitude ascents upon Mt. Everest had essentially normal cognitive function while they had extremely low PaO2 values at altitude. We will also review data on the longer term effects of both acute and chronic hypoxia on brain function, including data suggesting that several sub-regions of the hippocampus important for declarative memory are also extremely sensitive to hypoxia, and to a greater extent than other brain regions. We will the discuss the idea that these data imply that acute and chronic hypoxia may have differential effects upon different human cognitive functions, with anterograde memory (i.e. the ability to form new long term memories) as the human cognitive function that may be most sensitive to hypoxia. We will then discuss the data on correlations between intraoperative hypoxia and hyperoxia with POCD/delirium parameters, and review how optimizing intraoperative respiratory function (and oxygenation) can help avoid POCD/delirium and other postoperative cognitive problems.

After covering intraoperative hemodynamic and respiratory physiology, we will then shift our focus towards the relationship between intraoperative cerebral physiologic management and POCD/delirium risk and parameters. This section of the talk will focus on methods to monitor both cerebral perfusion itself, as well as cerebral electrophysiologic function and intraoperative embolic load, and the relationship between these measurements and POCD/delirium risk and parameters. We will discuss different ways of measuring cerebral electrophysiologic function, and data suggesting that the data from such monitors are affected not only be the anesthetic drugs administered (and the doses of these drugs) but also by patients' baseline neurocognitive function. We will also discuss data showing that some of the commercially available processed EEG monitors display altered

values in older adults, which raise questions about the use of some of these monitors in older adults. Finally, we will discuss data from several recent trials that have evaluated different EEG based monitor-based anesthetic titration protocols, and the effects of these protocols upon patient outcomes including POCD and delirium parameters. At the end of this talk, attendees should understand the current state of the art of intraoperative physiologic management to prevent postoperative delirium and POCD.

ANESTHESIOLOGY 2017
BOSTON OCTOBER 21-25

Preoperative Screening of the Older Surgical Patient: Cognition and Frailty

Gregory Crosby, MD & Deborah J. Culley, MD **Boston, MA**

Older patients account for over one-third of surgical procedures and, on a per capita basis, are nearly 3-times more likely than a middle-aged person to have surgery. They also have a disproportionately high morbidity, particularly with respect to postoperative cognitive outcomes. As such, there is growing interest in screening older patients preoperatively to identify those at high risk for developing delirium or other adverse cognitive outcome so the information can be factored into the planning and execution of surgical, anesthetic, and postoperative care. This, of course, is not a new idea.[1] Most patients scheduled for elective surgery have a preoperative assessment with those same goals in mind. But we typically do not formally assess for age-related conditions such as cognitive decline and frailty, which are common in older persons, during the standard preoperative evaluation. This review will focus on why these conditions are important in the surgical setting and how one might identify them in the older person preoperatively.

Cognitive impairment and postoperative outcomes

The older brain is fundamentally different from a younger one. Even a healthy older brain shrinks and these volumetric changes accelerate as we get older, with areas involved in memory, processing speed, and executive function being most severely affected.[2] Superimposed age-related brain disease can make matters worse. Seven-18% of persons age 60 or older have an asymptomatic brain infarct on MRI and 3-8% have unrecognized white matter lesions.[3] Moreover, dementia-like pathology, such as amyloid deposits and tau tangles, can be present in the brain long before—possibly decades before—clinical symptoms develop.[4] It should not be surprising then that cognitive impairment is prevalent in community dwelling older persons. Indeed, although estimates vary widely, about 5-20% of persons > 65 years of age have mild cognitive impairment (MCI), a widely accepted neurological syndrome defined as cognitive decline greater than expected for an individual's age and education[5, 6]
that does not interfere with activities of daily living. The point is that an older patient coming for elective surgery may be cognitively vulnerable, or even have cognitive deficits before surgery.

But we usually do not know about or suspect these problems because structured preoperative screening is typically not performed. Chronological age is a notoriously poor proxy for cognitive function and the casual, unstructured interview is insensitive.[7] In fact, healthcare professionals often miss mild forms of cognitive impairment because the symptoms are mild and daily functioning is intact and sometimes do not even recognize dementia.[8]

Why should we care? Cognitive status matters because impairment is associated with increased risk for both short- and long-term medical complications in geriatric surgical patients.[7] Preoperative cognitive impairment is a particularly strong predictor of postoperative delirium and may also play a role in development of POCD[9, 10] Furthermore, it is associated with postoperative non-cognitive complications too, including longer hospital stay, higher rate of discharge to an institutional care facility, higher 30-day readmission rate, and a higher six-month mortality.[11] Our challenge therefore is to identify those who are vulnerable. There is presently no "best" way but, fortunately, there are some practical options.

Preoperative cognitive screening.

Conventional neuropsychological testing is a lengthy, time-consuming process but brief screening tools exist and some have been tested in the preoperative setting. The Mini Mental Status Exam (MMSE) may be somewhat familiar because it is often used in research studies but, at 30 items and 7-10 min to complete, is too long for most high-throughput clinical settings. The Montreal Cognitive Assessment (MoCA) is likewise 30 items and takes about 10 min and has been used preoperatively, though not for routine clinical screening.[12] The Mini-Cog, which combines clock drawing and 3-item recall, is another. It tests executive function and memory, takes just 2-3 min to complete, is easy to administer and score, and is relatively free of education bias. Another is the animal fluency test (AFT). All that is required here is that the individual name as many animals as possible in 60 seconds, so no special expertise is required

and scoring is easy. Although the numbers vary with the screening test used, type of surgical procedure, and age of the patients, somewhat remarkably between 20-68% of patients > 65 years of age screen positive for cognitive impairment before surgery.[11, 13-15] What's more, several studies show that that poor performance on a preoperative cognitive screening test is associated with an increased incidence of postoperative delirium, medical and surgical complications, discharge to an extended care facility, and 6-month mortality.[11, 13][14, 15] For these reasons, a joint statement of the American College of Surgeons and the American Geriatric Society recommends that preoperative cognitive assessment be performed.[16]

That said, there are some important caveats to consider. A single screening test cannot diagnose MCI or dementia and the sensitivity and specificity of these tests are not perfect (e.g. MiniCog 99 and 93%, AFT 84 and 75%, respectively). Therefore, there will be false positives, so one must be careful not to oversell or misinterpret the results. Some tests have an education, age, or language bias and may not have normative data available.[17] Some are easy to administer but difficult to score reliably and no studies have directly compared the various brief instruments to determine which is best for identifying impairment and predicting outcomes in a surgical setting. Finally, the biggest challenge is that there is as yet little evidence that changing care for elective surgery based on results of preoperative cognitive screening improves geriatric surgical outcomes, although recent work in traumatized older patients provides reason for optimism.[18]

Frailty and Postoperative Outcomes

Frailty, defined as age-related decline in functional status, is another common geriatric syndrome that may affect surgical outcome. Definitions vary but frailty is characterized by loss of physiologic reserve in multiple organ systems and poor resistance to stressors.[19] It has physical, cognitive, functional, and emotional features, which make it somewhat vague and difficult to define objectively. Unlike cognitive impairment, however, frailty is relatively easy to recognize. It is also common in the community, with about 45% of older persons having some signs and 10% having the full-blown syndrome. Not surprisingly, a similar fraction of older elective surgical patients have the syndrome. This becomes important because frailty is associated with increased risk of postoperative complications, including delirium, and longer hospital length of stay, a decreased likelihood of discharge to home, higher 30-day readmission, and higher six-month mortality rates.[19-21] Specifically, the complication rate among frail patients, defined by age, activities of daily living, MiniCog score, Charlson co-morbidity index, ASA score, history of falls, anemia, serum albumin level, and a timed mobility test, is nearly 3X higher (58% vs. 21%) than non-frail patients. This suggests the preoperative evaluation of older patients should include some measure of frailty. The problem, however, is that there is no standard way to measure it, although a few scales have been used preoperatively.

Preoperative screening for frailty

Frailty indexes typically cover cognition, function, nutrition and weight loss, weakness / exhaustion, co-morbidities, falls, emotion (depression), and social vulnerability using self-report questionnaires and objective tests. In general, the multicomponent instruments sum a list of deficits in an individual patient to yield a frailty score, but can be time consuming.[19]

The Fried Frailty Phenotype is considered the standard,[22] and many frailty indexes are adaptations of the Fried. This index asks about unintentional weight loss, depression, and activity but also objectively measures grip strength and walking speed. The Edmonton Frail Scale assesses characteristics including cognition, general health status, functional independence, functional report, social support, medication use, nutrition, mood, and continence. It also includes a functional measure called the 'Get Up and Go Test', which is a timed test that requires the patient to stand up from a chair and walk ten feet and then return to sit in the chair. A variation, the Reported Edmonton Frail Scale, replaces the 'Get Up and Go' test with patient report of physical function before the current illness. Another tool is the SHARE Frailty Instrument. This instrument has a separate scale for males and females, as some data suggest females are more likely to develop frailty, and relies on self-reported information (exhaustion, weight loss, slowness, low activity) except for objectively measuring grip strength. Some studies utilize a combination of these measures and also ask about falls and include medical data that would be routinely evaluated during a preoperative appointment.[19, 20] Time is an issue for all of these, with some multicomponent instruments requiring 10-15 min. In contrast, the Frail

Scale,[23] which asks about fatigue, resistance (stair climbing), ambulation, illnesses, and loss of weight, takes just 1-5 min and so is well suited to use in a preoperative evaluation clinic.

Unsurprisingly, many elective surgical patients satisfy criteria for frailty and low scores on these assessments are associated with adverse geriatric health outcomes. For example, depending on the definition, 35-41% of elective orthopedic surgery patients classify as frail and they stay longer in the hospital, have more complications, and are more likely to go to a postacute care facility upon discharge.[24] Similarly, frailty is associated with delirium and mortality after cardiac surgery.[25, 26] but, due to heterogeneity of assessments and limited generalizability, the quality of evidence linking it to mobility or disability outcomes is moderate and low for mortality. In lieu of multicomponent instruments, single variables such as mobility, walking speed, and falls also appear to be useful for predicting adverse postoperative events. For instance, self-reported poor mobility or a history of a fall are associated with more postoperative complications, discharge institutionalization, and hospital readmission.[27-29] Finally, parameters that approximate frailty and can auto-populate from an electronic medical record (demographics, BMI, lab data, ASA score) can predict major complications and 30-day mortality,[30] suggesting that even routinely collected preoperative data can provide insight into geriatric surgical risk.

Conclusion

Cognitive impairment and frailty are prevalent in older persons and are associated with an adverse effect on surgical outcomes, and delirium in particular. Yet, geriatric surgical patients are not routinely evaluated for these conditions preoperatively. There are simple, brief tools for doing so and recent studies suggest it is feasible to incorporate them into the preoperative visit and that doing so can help risk stratify older surgical patients. Studies demonstrating that such testing can be leveraged to improve geriatric surgical outcomes are few, however, making this a fertile area for research.

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Postoperative Delirium: Be afraid of confusion

Edward R. Marcantonio, MD SM **Boston, Massachusetts**

INTRODUCTION and NOMENCLATURE

Delirium has been described in the medical literature for more than two thousand years. Despite this, it remains under-recognized and often inappropriately evaluated and managed. Up to 30 synonyms for delirium exist in the peer-reviewed literature. *Acute confusional state* is the most common synonym, and the term still preferred today by some specialties. Other common synonyms include *altered mental status* and *toxic/metabolic encephalopathy*. Delirium can be thought of as acute brain failure[1], and is the final common pathway of multiple mechanisms, similar to acute heart failure. The official definition for delirium in DSM5 requires a disturbance in attention and awareness that develops acutely and tends to fluctuate[2]. The term postoperative delirium is used for any delirium that occurs in the post-surgical period, even if it is ultimately attributed to other factors besides surgery and anesthesia[3].

INCIDENCE AND RISK FACTORS

Delirium is the most common complication after surgery in older adults[3]. The incidence is 15-25% after elective non-cardiac surgery, and up to 50% after high-risk procedures such as hip fracture repair, aortic aneurysm repair, and coronary artery bypass grafting. In a prospectively validated clinical prediction rule for delirium after elective noncardiac surgery, seven risk factors were identified preoperatively: advanced age, cognitive impairment, physical functional impairment, history of alcohol abuse, markedly abnormal serum chemistries, intrathoracic surgery, and aortic aneurysm surgery[4]. Patients with none of these risk factors had a 2% risk of delirium, those with one or two risk factors had a 10% risk, and those with three or more risk factors had a 50% risk. More recently, a clinical prediction rule for delirium after cardiac surgery has been validated. Four risk factors were identified: cognitive impairment, history of stroke or transient ischemic attack, depressive symptoms, and low or high albumin[5].

In addition to baseline risk factors, intraoperative and postoperative management plays an important role in the development of delirium. Multiple studies demonstrate that the type or route of intraoperative anesthesia, whether general, spinal, epidural, or combined, has little impact on the risk of delirium[6]. However, the total dose of anesthetic agents may play an important role and efforts to reduce, or titrate this dose to the lowest effective amount may reduce delirium. For instance, a randomized trial used bispectral (BIS) monitoring to titrate the dosage of intraoperative sedative medications among hip-fracture patients undergoing surgical repair using spinal anesthesia. Patients in the low-dose arm had a markedly reduced rate of postoperative delirium relative to the high-dose arm (19% versus 40%, $P<.01$)[7].

Postoperative medication management also plays an important role in delirium. Postoperative use of benzodiazepines and certain opioids, especially meperidine, is strongly associated with the development of delirium[8]. Although pain medications can cause delirium, adequate pain management is also important, because high levels of postoperative pain have also been associated with delirium[9]. Strategies to provide adequate analgesia with minimally effective doses of opioids should be used. These include the use of scheduled rather than as-needed dosing, patient-controlled analgesic pumps, regional analgesia, opioid-sparing analgesics, and non-pharmacologic approaches, such as ice packs. Low postoperative hematocrit level (<30%) has also been associated with postoperative delirium, although transfusions have not been shown to reduce delirium[10].

DELIRIUM IS DISTINCT FROM "POCD"

Postoperative cognitive dysfunction (POCD) is a phenomenon that has received considerable attention, with a particular focus on long-term POCD after cardiac surgery. As opposed to delirium, POCD does not have *DSM5* diagnostic criteria, nor does it have ICD-associated "disease" codes. POCD is usually defined by declining

performance on serial testing with a neurocognitive battery, although there is little consensus as to how to operationalize this measurement[11]. Interestingly, many studies of POCD have not included good measures of delirium, and many studies of postoperative delirium do not measure POCD. Results from studies that have both measures well integrated are just emerging. These suggest that delirium and POCD are associated, but do not fully explain each other—that is, some patients with delirium do not go on to develop POCD, and some patients who develop POCD did not have delirium. Recently, a new nomenclature has been proposed changing the term "POCD" to postoperative neurocognitive disorder (major and minor) to align more closely with the new terms being used for dementia and mild cognitive impairment, respectively.

PROGNOSIS, RELATIONSHIP WITH DEMENTIA

Evidence is mounting that delirium is strongly and independently associated with poor patient outcomes. A meta-analysis that included almost 3,000 patients followed for a mean of 22.7 months demonstrated that delirium was independently associated with an increased risk of death (OR 2.0; 95% CI, 1.5–2.5), institutionalization (OR 2.4; 95% CI, 1.8–3.3), and dementia (OR 12.5; 95% CI, 11.9–84.2) [12]. The last finding requires further explication. While dementia is an established risk factor for delirium, evidence is increasing that the relationship may be bidirectional[13]. Three recent landmark studies described below seek to clarify whether delirium is merely the herald of previously unrecognized cognitive impairment (or other brain vulnerability), or whether the delirium itself sets forth a CNS process that accelerates onset of dementia.

A 2012 study examined the 1-year cognitive trajectories of older cardiac surgery patients and found that delirium is associated with an acute decline in cognitive function and persistent deficits. Patients who did not develop delirium returned to their preoperative cognitive baseline by 1 month after surgery, while those with delirium had not returned to baseline 1 year after surgery[14]. A 2013 study measured cognitive function in survivors of an intensive care unit stay 1 year later, and found that 24% these patients were functioning at or below the level of patients with mild Alzheimer's Disease[15]. This study was not restricted to older adults, and this level of cognitive dysfunction was seen in all age groups (down to 18-45 years) and all levels of comorbidity. Finally, 2016 study of 560 dementia-free older adults underdoing major non-cardiac surgery found that delirium was associated with an acute decline in cognitive function, recovery by 2 months, and then an accelerated downward slope of cognitive function over the next 1.5-3 years[16]. Taken together, this evidence suggests that delirium is not just an unmasking of latent dementia or Alzheimer's Disease, and therefore that efforts to prevent and treat delirium (see below) may have a significant public health impact by reducing the burden of cognitive impairment among older adults.

DIAGNOSIS AND CASE-FINDING FOR DELIRIUM

Under-recognition of delirium is a major problem, with less than 50% of all cases recognized in routine care. Systematic reviews have recommended the Confusion Assessment Method (CAM) as the most useful bedside assessment tool for delirium[17]. By judging the presence or absence of the four key CAM features: 1) Acute change or fluctuating course, 2) Inattention, 3) Disorganized Thinking, and 4) Altered Level of Consciousness, clinicians can establish the diagnosis of delirium[18]. Use of formal mental status evaluation greatly improves detection and reliability of the CAM assessment. Over the past few years, several brief assessment tools have been developed to operationalize the CAM. One, the 3D-CAM, has been validated against a clinical reference standard in older general medical patients, and had 95% sensitivity and 94% specificity [19]. 3D-CAM should be equally applicable in an older surgical population. Among surgical intensive care unit patients, the CAM-ICU is the CAM assessment of choice[20].

To improve recognition of delirium, medical centers are starting to use standardized tools to screen high-risk patients, such as those in the ICU and after major surgery. Such screening is particularly important for identifying cases of hypoactive delirium, which might otherwise go unnoticed by the care team. A brief but standardized screening assessment should be administered on a daily basis, or even more frequently. Frequent standardized assessment and documentation of mental status is also important to allow detection of acute changes and fluctuations, which are a key feature of delirium. There is no consensus how to best implement widespread screening for delirium. Importantly, such screening needs to be coupled with education on best practices of delirium management (see below); otherwise, patients could be harmed, rather than helped, by such programs.

DELIRIUM PHENOMENOLOGY

The classic presentation of delirium is thought to be the extremely agitated patient. However, agitated, hyperactive, or mixed delirium represents only 25% of cases, while the remainder have hypoactive ("quiet") delirium[21]. Evidence suggests that hypoactive delirium is associated with an equal or poorer prognosis than delirium with hyperactive or normal psychomotor features. Potentially, one of the reasons for this poorer prognosis is that hypoactive delirium is less frequently recognized. As described above, special case-finding efforts are necessary to detect quiet delirium.

Although we often speak of delirium as being either present or absent, the number and severity of symptoms vary widely. To more completely describe delirium, several severity scales have been validated and published. The most recent scale, termed CAM-Severity (or CAM-S), is derived directly from the Confusion Assessment Method and has both a long form that uses all 10 CAM delirium features (scored 0-19, 19 worst) and a short form that uses only the 4 CAM diagnostic features (scored 0-7, 7 worst)[22]. The CAM-S has excellent predictive validity (incremental beyond diagnosis) for several important clinical and health utilization outcomes. Patients who have some delirium features, but do not meet all diagnostic criteria, have subsyndromal delirium, which has also been shown to be associated with poor outcomes, though not as bad as full delirium.

NEUROPATHOPHYSIOLOGY OF DELIRIUM

One of the best-documented mechanisms of delirium is cholinergic deficiency. This is seen classically in overdoses of anticholinergic medications such as atropine, which in severe cases can be reversed by administration of physostigmine. In addition, many medications not classified as anticholinergic (eg, antihistamines, certain opioids, and antidepressants) have substantial anticholinergic activity and can also precipitate delirium. Indices have been developed that enable clinicians to estimate the anticholinergic burden of a patient's medication regimen. Despite their potential ability to reverse cholinergic deficiency, the cholinesterase inhibitors donepezil , rivastigmine, and galantamine have not been effective for either the prevention or treatment of delirium.

A second potential mechanism of delirium is inflammation, which can be particularly important in postoperative patients and in those with cancer or infection. A growing body of literature has documented an association of delirium with increased levels of inflammatory markers, including C-reactive protein, interleukin-1β and 6, and tumor necrosis factor α. Inflammation can break down the blood-brain barrier, allowing toxic medications and cytokines greater access to the CNS. Once in the CNS, inflammation can cause direct toxicity to neurons, which may explain increased levels of neuronal injury markers such as S-100β in the serum of patients with delirium, and also the potential link between delirium and long-term cognitive dysfunction [3].

Animal models may advance our understanding of delirium mechanisms. One exciting development in this area is the analogy of delirium to "sickness behavior syndrome[1]. In this syndrome, animals exposed to certain anesthetics, surgery, or other inflammatory stimulants manifest symptoms similar to hypoactive delirium—they stop eating, have reduced movements and ineffective interactions with the environment. Scientists are now examining what is going on in the brains of such affected animals with a goal of better understanding delirium.

Advances structural and functional neuroimaging provide another opportunity for advancing our knowledge of delirium pathophysiology. It is challenging to image patients in the middle of the delirium episode, so many studies have focused on imaging before and after delirium. Preliminary evidence suggests that delirium may lead to a state of neuronal pathway disconnectivity[1], potentially explaining the residual cognitive dysfunction following delirium.

Finally, new generation neurophysiology techniques, including dynamic intraoperative electroencephalography, and transcranial magnetic stimulation, are being applied to better understand mechanisms of delirium.

EVALUATION AND MANAGEMENT

All patients with newly diagnosed postoperative delirium require a careful history, physical examination, and targeted laboratory testing[23]. Most treatable causes of delirium lie outside the CNS, and these should be investigated first. Moreover, multiple contributing factors are often present, so the diagnostic evaluation should not be terminated because a single "cause" is identified. The history should focus on the time course of the changes in mental status and their association with other symptoms or events (eg, fever, shortness of breath, medication change). Because medications are the most common and treatable cause of delirium, a careful medication review is imperative. The physical examination should include vital signs and oxygen saturation, a careful general medical examination, and a neurologic and mental status examination focusing on tests of attention. The emphasis should be on identifying modifiable medications and new medical complications that might be contributing to delirium.

Laboratory tests and imaging studies should be selected on the basis of history and examination findings. Most patients require at least a CBC, electrolytes, and kidney function tests. Urinalysis, tests for liver function, serum medication levels, arterial blood gases, as well as chest radiographs, an ECG, and appropriate cultures are helpful in selected situations. Cerebral imaging is often performed but is rarely helpful, except in cases of new focal neurologic findings. In the absence of seizure activity, meningeal signs, or surgical CNS manipulation, electroencephalograms and cerebrospinal fluid analysis rarely yield helpful results.

The delirious patient is susceptible to a wide range of iatrogenic complications, and careful surveillance is critical. Bowel and bladder function should be monitored closely, but urinary catheters should be avoided unless absolutely required for monitoring fluids or treating urinary retention. Bowel stimulants and fecal softeners can be used to prevent obstipation, particularly in those who are concomitantly using opioids. Complete bed rest should be avoided, because it can lead to increasing disability through disuse of muscles and the development of pressure ulcers and atelectasis. Physical exercise and ambulation prevent the deconditioning often associated with hospitalization. Malnutrition can be avoided through careful attention to intake of food and fluids. Some delirious patients may need assistance for eating.

MANAGING BEHAVIOR IN DELIRIUM

Non-pharmacological interventions are the cornerstone of behavior management in delirium[3,23]. The patient should be placed in a room near the nursing station for close observation. Orienting items such as clocks, calendars, and even a window view should be made available. Patients should be encouraged to wear their eyeglasses and hearing aids. Physical restraints, which are often justified as a means to reduce the risk of patient self-injury, have actually been associated with increased injury. On the regular medical and surgical wards, use of restraints should be reduced, if not eliminated. In the intensive care unit (where 1:1 or 1:2 nursing is available), restraints may be required to prevent the removal of important devices, such as endotracheal tubes, intra-arterial devices, and central intravenous catheters. Whenever restraints are used, the indicators for use should be frequently reassessed, and the restraints should be removed as soon as possible.

Medications used as chemical restraints extract a costly toll in accidents, adverse events, and loss of mobility and should also be avoided if possible. Pharmacologic intervention may be necessary for symptoms such as delusions or hallucinations that are frightening to the patient when verbal comfort and reassurance are not successful. Some delirious patients display behavior that is dangerous to themselves or others and cannot be calmed by a family member or aide. Similar to physical restraints, indications for pharmacologic intervention should be clearly identified, documented, and constantly reassessed. Daily renewal of orders for physical or chemical restraints is one way of ensuring that they are stopped when no longer needed.

The literature on pharmacological management of delirium is growing rapidly and can be summarized as follows: 1) Except in unusual cases (e.g. alcohol withdrawal delirium), antipsychotics have a more favorable risk:benefit ratio

than benzodiazepines or other sedatives. 2) All use of antipsychotics for delirium is off-label—there are no FDA approved drugs for the indication of delirium. 3) Many drug treatment and prevention studies were conducted in mixed age groups in the intensive care unit; it is unclear whether the risk:benefit ratio for use of these drugs are similar in older patients on the general surgical wards. 4) Many studies are not blinded, not placebo controlled, or corporate sponsored, raising concerns about validity. 5) The outcome of some studies is delirium severity; yet, existing delirium severity scales tend to overweight hyperactive symptoms, so that converting hyperactive delirium to hypoactive delirium (which has worse outcomes, as noted above) is measured as a reduction in severity.

A recent meta-analysis reviewed 12 randomized trials of antipsychotics for delirium treatment, and found that they did not reduce delirium duration or severity, ICU or hospital length of stay, or mortality[24]. Thus, the decision whether to use antipsychotics involves a trade-off between immediate reduction of agitation, hallucinations, and delusions versus risk of sedation and antipsychotic-induced complications[23]. If treatment with antipsychotics is warranted, the choice of agent is often made based on side effects. Drugs such as haloperidol and risperidone have the least sedation but greatest risk of extrapyramidal side effects (EPS), while quetiapine is most sedating and has the least EPS. The availability of intravenous dosing may be important for patients in the ICU. Regardless of the drug selected, the initial dose should be as low as possible, as there is a wide variability in patient responses to these drugs. More drug can always be administered; once administered, it cannot be taken away. For the most part, dosing in delirium (as opposed to dementia with behavioral disturbances) is on an as needed basis, although patients with prolonged delirium with behavioral symptoms may need continuous scheduled dosing. As noted above, these drugs should be stopped as soon as possible. In the rare circumstances that they are needed beyond hospital discharge, clear parameters for their discontinuation should be included in the discharge paperwork.

DELIRIUM EDUCATION (FOR FAMILY MEMBERS)

It is important to stress to family members that delirium is usually not a permanent condition, but rather that it improves over time. Unfortunately, as described above, persistence of delirium symptoms is common. Thus, when counseling families, it is important to point out that many cognitive deficits associated with the delirium syndrome can continue, abating weeks and even months after surgery. Careful monitoring of mental status and providing adequate functional supports during this period are necessary to give the patient the maximal chance of returning to his or her baseline level. Family members can play an important role in the hospital and postacute setting by providing appropriate orientation, support, and functional assistance. Hospitals are increasingly making provisions for family members to sleep overnight with relatives who are already delirious or at high risk of developing delirium. While symptoms of delirium may persist, acute exacerbation of cognitive dysfunction is not expected during the convalescent period and therefore likely heralds a new medical problem. Families should be counseled to seek prompt medical attention if a patient's mental status acutely worsens.

DELIRIUM PREVENTION

A 2015 meta-analysis examined the effectiveness of multifactorial non-pharmacological interventions for delirium prevention such as the Hospital Elder Life Program (HELP)[25]. Fourteen high quality intervention studies were identified. Of these, 11 studies demonstrated significant reduction in delirium incidence, OR=0.47, 95% C.I. 0.38, 0.58, while 4 studies demonstrated significant reduction in hospital falls, OR=0.38; 95% CI, 0.25, 0.60. There were non-significant trends toward shorter hospital length of stay and reduced need for post-acute facility placement. This meta-analysis provides strong evidence for the use of non-pharmacological prevention strategies in delirium.

Another effective non-pharmacological approach for delirium prevention is proactive geriatrics consultation in high risk surgery patients. Consultation begins preoperatively and continues throughout the hospitalization, with daily recommendations based on a structured protocol. A randomized controlled trial performed in older hip fracture patients demonstrated that this model can reduce delirium--the consultation group achieved 36% reduction in delirium incidence (NNT=5.6)[26]. Geriatrics-orthopedics services have been widely adopted for hip fracture patients.

The effectiveness of pharmacological approaches for delirium prevention is less clear. The same meta-analysis cited above examined seven studies that tested low-dose antipsychotics for prevention of delirium in high risk surgical

patients[24]. There were no significant differences in delirium incidence (pooled OR = 0.56, 95% CI = 0.23–1.34), ICU or total hospital length of stay, and mortality.

QUALITY MEASURES AND CONSENSUS GUIDELINES

Recently, the American Geriatrics Society Section for Enhancing Geriatric Understanding and Expertise among **Surgical** and Medical Specialists (**SEGUE**) released guidelines for the prevention and management of postoperative delirium [27]. The level of evidence supporting various recommendations varies widely, from consistent randomized trials to a reliance on best clinical practices, and is reflected in the strength of the recommendations provided in the guideline. Major elements of the guidelines are summarized in the Table (next page), which also serves as a good summary of the key points in this article.

Table: American Geriatrics Society Guidelines for Postoperative Delirium

Eight strong recommendations: benefits clearly outweighed the risks, or the risks clearly outweighed the benefits.

- Multicomponent nonpharmacologic interventions delivered by an interprofessional team should be administered to at-risk older adults to prevent delirium.
- Ongoing educational programs regarding delirium should be provided for health care professionals.
- A medical evaluation should be performed to identify and manage underlying contributors to delirium.
- Pain management (preferably with non-opioids) should be optimized to prevent postoperative delirium.
- Medications with high risk of precipitating delirium should be avoided.
- Cholinesterase inhibitors should not be newly prescribed to prevent or treat postoperative delirium.
- Benzodiazepines should not be used as first-line treatment of agitation associated with delirium.
- Antipsychotics and benzodiazepines should be avoided for treatment of hypoactive delirium.

Three weak recommendations: current level of evidence or potential risks of the treatment did not support a strong recommendation:

- Multicomponent non-pharmacologic interventions implemented by an interprofessional team may be considered when an older adult is diagnosed with postoperative delirium to improve clinical outcomes.
- The injection of regional anesthetic at the time of surgery and postoperatively to improve pain control with the goal of preventing delirium may be considered.
- The use of antipsychotics (eg, haloperidol, risperidone, olanzapine, quetiapine, or ziprasidone) at the lowest effective dose for at the lowest effective dose for the shortest possible duration may be considered to treat delirious patients who are severely agitated or distressed or who are threatening substantial harm to self and/or others.

One “insufficient evidence” recommendation: current level of evidence or potential risks of the treatment did not support either a strong or weak recommendation:

- Use of processed electroencephalographic (EEG) monitors of anesthetic depth during intravenous sedation or general anesthesia may be used to prevent delirium.

Insufficient evidence to recommend either for or against the following:

- Prophylactic use of antipsychotic medications to prevent delirium
- Specialized hospital units for inpatient care of older adults with postoperative delirium

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Anesthetics Drugs, Depth, and Delirium

Pratik P. Pandharipande, M.D. **Nashville, TN**

Acute brain dysfunction can occur when there is an imbalance of the brain's homeostatic reserve and acute stressors, and refers to delirium, but may also include coma in the hospitalized patient. A comprehensive psychiatric evaluation using criteria based on the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), 5th edition,[1] is considered the gold standard for diagnosing delirium and includes sudden onset of altered consciousness, reduced capacity to maintain one's attention and awareness, and disorganized thought process, all of which cannot be better explained by another neurocognitive disorder or severely reduced arousal. Postoperative delirium (POD) is recognized as a subset of delirium in the tenth edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) system.

A delirium diagnosis identifies the constellation of acute brain dysfunction signs but does not identify the etiology. It should, therefore, prompt further investigation into potential risk factors for delirium. Delirium risk factors are numerous and can be stratified into predisposing and precipitating factors. Diminished preoperative cognitive status is probably the biggest risk factor for delirium in the elderly population.[2] Age >75 years and cerebrovascular disease have also been identified as risk factors for delirium, specific to the elderly.[2] Frailty, which is common in the elderly and refers to critically reduced or impaired functional reserves that may involve multiple organ systems, has been shown to be independently associated with a greater risk of developing delirium.[3-5] Other risk factors for delirium include lower levels of education, major comorbid disease, major surgery, acute renal failure, vision or auditory disturbances, alcoholism, infection, and electrolyte disorders.[6,7] Use of physical restraints, use of urinary catheters, malnutrition, and acute pain have also been reported as risk factors.[8] High and low mean arterial pressures, as well as overall blood pressure fluctuation, have been associated with increased risk of delirium, but the optimal blood pressure target has not been determined with regard to delirium.[9-11]

Sedative medications such as benzodiazepines and opioids have been associated with delirium; longer acting benzodiazepines and opioids with active metabolites[12] and infusion are more likely to be associated with increased risk of delirium.[13-15] Deep levels of sedation also carry a higher risk of delirium.[13] Minimizing opioids, benzodiazepines, and anticholinergics is therefore often a mainstay of delirium management.[16] While adequate pain control is paramount to delirium prevention, opioid sparing techniques using multimodal analgesia pain regimens and regional anesthesia techniques should be employed, to achieve adequate pain control, while minimizing opioid use. Of the opioid options, meperidine has been shown to have a higher risk of delirium.[17] Dexmedetomidine has also been shown to reduce delirium incidence, duration, ICU length of stay, and cost when compared to propofol when used in postoperative cardiac surgery patients.[18] A few recent trials have shown low-doses of dexmedetomidine to prevent delirium when compared to either placebo or propofol in subsets of postsurgical patients,[18-20] and it is now recommended by the European Society of Anaesthesiology as an intraoperative adjunct for prevention of elderly patients at high risk for delirium.[21]

General anesthetics have been hypothesized to contribute to both postoperative cognitive dysfunction and dementia but the evidence is inconsistent, and clear causal association has yet to be established.[22-25] With regard to the role of anesthesia in the development of POD, studies

monitoring electroencephalogram (EEG) during general anesthesia have shown that current recommended doses of anesthetics for elderly patients may be placing them into a profound state of brain inactivation known as burst suppression.[26,27] Titration of anesthetic doses based on real time EEG monitoring has been associated with reduced POD likely from reduced over sedation.[28] Monitoring of anesthetic depth and avoidance of deep anesthesia in the elderly, is considered part of delirium prevention strategies.[29]

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Surgical Fire: Awareness, Prevention and Management

Mark C. Phillips, MD **Birmingham, Alabama**

Awareness

Surgical fires are a serious and potentially catastrophic event in the operating room. The Emergency Care Research Institute (ECRI) estimates that there are 550-600 surgical fires in the United States each year.[1] The exact incidence is unknown as half of the states do not require mandatory reporting. A number of patients suffer severe burn injuries each year, and there are fatalities reported from burn injuries incurred in the operating room. Fires occur on the body or in the airway during surgical procedures in the airway. There are also fires that occur in the operating room not related to the surgical procedure. Fires on the body during procedures in the head and neck area, especially done under monitored anesthesia care (MAC) anesthesia are the most frequently occurring today.[2]

Much attention has been directed over the last several years toward educating anesthesiologists, nurse anesthetists, nursing personnel, and surgeons regarding the risks of surgical fires and means of preventing them. In 2003 the Joint Commission published a sentinel event alert: Preventing Surgical Fires. In 2005 the AORN published a Position Statement on Fire Prevention. In 2008 the American Society of Anesthesiologists (ASA) published a Practice Advisory for the Prevention and Management of Operating Room Fires which was updated in 2013. This was designed to provide information to help prevent operating room fires, and identify the proper response to an operating room fire. The American College of Surgeons has conducted educational sessions on surgical fire prevention at its annual meeting. The FDA introduced the Preventing Surgical Fires Initiative. The Anesthesia Patient Safety Foundation has published a Fire Prevention Algorithm as well as an educational video. Yet despite these efforts, surgical fires continue to occur.

When considered in light of the 50-60 million surgeries performed each year, surgical fires are relatively rare. However, when surgical fires do occur, the results can be devastating with disfiguring burn injuries, psychological trauma, medical malpractice litigation, and death. Continuing education efforts are warranted in order to decrease the incidence of these events.

In order for a fire to occur, three factors must be present. These are an oxidizer, an ignition source and fuel. Together these constitute the three components of the fire triangle. Elimination of one component of the fire triangle breaks the triangle and greatly reduces the risk of fire.

Oxidizers are oxygen and nitrous oxide. An oxygen enriched atmosphere increases the likelihood and intensity of combustion. An oxygen concentration greater than 21% produces an oxygen enriched atmosphere. Many materials that are not susceptible to combustion in room air will burn in an oxygen enriched atmosphere. Oxygen enriched atmospheres lower the temperature at which fuels ignite and allow fires burn more intensely and to spread faster.[3] Due to this intensity and fast spread, operating room fires can cause serious injury very rapidly before the team can respond. Thus the importance of prevention.

Oxygen can be delivered via nasal cannula, face mask, laryngeal mask airway, or endotracheal tube. The risk of fire is higher when a nasal cannula or face mask is used to deliver oxygen. Oxygen is heavier than air and so will settle in low lying areas such as beneath surgical drapes. Nitrous oxide mixed with oxygen is also an oxygen enriched environment. Fire liberates oxygen from nitrous oxide allowing it to support combustion. The risk of fire with a nitrous oxide-oxygen mixture is considered equivalent to a 100% oxygen environment.[3]

The second component of the fire triangle is an ignition source. The most common ignition source in the operating room is the electrosurgical unit (ESU). Other ignition sources include lasers, heated probes, drills and burrs, and fiberoptic light sources and defibrillators.[3]

The third component of the fire triangle is a fuel source. Fuel sources include anything that can burn. The most common fuel sources are surgical drapes, gowns, sponges, linens, and dressings. Other fuel sources include nasal

cannulas, face masks, endotracheal tubes, blood pressure cuffs and the patients' hair.[3] The vapors of alcohol containing surgical prep solutions are also a fuel source and can be very flammable.[2]

Each member of the surgical team controls a specific side of the fire triangle. The surgeon controls the ignition source. The nurse controls the fuel. The anesthesiologist controls the oxidizers.

Prevention of Surgical Fires

All members of the surgical team are responsible for preventing surgical fires and need to be proactive in taking proper precautions to see that the risk of surgical fire is minimized as much as possible. Cornerstones of fire prevention include preparation, fire risk assessment and communication.

Safety measures should be undertaken before a patient is brought to the operating room. These measures include checking the availability of fire safety equipment. OR personnel should know the location of fire extinguishers, fire alarms and medical gas shut off valves. Sterile saline, flashlights, self-inflating bag-valve masks, and extra breathing circuits should be in place in the operating room.[4]

An assessment of fire risk is recommended as part of the surgical time out. A fire risk assessment score was developed by the Christiana Care Health System that stratifies risk on a scale of 0 to 3. One point is allocated for each of the following: A. surgical site or incision above the xiphoid. B. open oxygen source, for example, patient receiving oxygen via face mask or nasal cannula. C. planned use of an ignition source such as ESU or laser. If the assessment produces a score of 3 this is considered high risk and the OR team should develop a plan to minimize risk. A score of two is low risk with potential to convert to high risk. A score of zero or one is low risk.[5]

Communication among the members of the OR team is critically important in lessening the risk of surgical fires. During MAC cases, especially cases involving the head and neck areas, it is important to keep the FiO_2 as low as possible. A patient receiving oxygen 2 liters/minute by nasal cannula via the auxiliary flow meter on an anesthesia machine is receiving less than 30% alveolar inspired oxygen. However, 100% oxygen is flowing from the nasal cannula and can accumulate under the drapes. Mixing air and oxygen to keep the FiO_2 less than 30% delivered to the patient and the operative site is desirable and will lessen the risk of a fire occurring.[6] If possible no supplemental oxygen during MAC cases is recommended. If a patient requires a large amount of sedation to tolerate the surgical procedure, and thus requires significant supplemental oxygen to maintain SaO_2 greater than 90%, then a general anesthetic utilizing a supraglottic airway or endotracheal tube is recommended.

The surgeon and anesthesiologist must communicate. The surgeon must know what oxygen supplementation is being given to the patient. The anesthesiologist must know when the surgeon is going to use the ESU. Oxygen must be reduced or turned off for several minutes before the surgeon plans to use the ESU. This allows the accumulated oxygen to dissipate. In draping the patent for the procedure, the surgeon should place the drapes to lessen the chance of oxygen accumulating under the drapes or flowing into the surgical site.[6] Drapes should be placed in an "open face" manner if possible. Another suggestion to reduce oxygen pooling while using supplemental oxygen via face mask or nasal cannula is to provide air via the anesthesia circuit to dilute the oxygen concentration.[7]

An analysis of operating room fires in the ASA closed claims database revealed that the use of the ESU was the most common ignition source, being responsible in 90% of fire claims. Oxygen served as the oxidizer in 95% of ESU induced surgical fires .[8] Ignition can occur when the ESU is activated in an oxygen enriched atmosphere. Ignition can also occur when the device is activated inadvertently while placed in contact with the surgical drapes. Whenever the ESU is not being used it should be placed in a holster away from the surgical site. The ESU should only be activated by the person using it. It should only be activated when the tips are in view and deactivated before removal from the surgical site. The tip can remain very hot for several seconds after it is deactivated. There have not been any fires reported with use of a bipolar ESU.[3] This is likely due to the low power and lack of arcing at the tip of the bipolar forceps. Having a basin of water or saline on the sterile field is recommended for any case in which an ESU is being used so that it can be immediately accessed to douse flames.

Fiberoptic light sources collect incandescent light energy and direct it into an optical fiber. Fiberoptic light sources can produce hundreds of watts of light power. This can ignite a fire. Steps should be taken to lower the risk of fire

with fiberoptic light sources. All cable connections should be completed before activating the source. The light source should be placed in standby or turned off before disconnecting. A fiberoptic light source or light cord should never be left in close proximity to surgical drapes while still turned on.[3]

While the ESU is the ignition source for the majority of surgical fires, lasers used in a variety of surgical procedures have been responsible for ignition in a number of surgical fires. Laser is an acronym for light amplification by stimulated emission of radiation. A laser has an energy source and a material known as the lasing medium that is energized by the energy source to emit light. Lasers emit coherent radiation. The light is monochromatic, coherent and collimated. The light beam does not disperse with distance. Lasers can focus into small spots with high power density. Various medical lasers are available. The neodymium-doped YAG (Nd-YAG) laser is the most powerful of the medical lasers. Tissue penetration is 2-6 mm and it is frequently used for debulking of airway and bronchi tumors. CO_2 lasers have little tissue penetration and are used when exact precision is required. CO_2 lasers are frequently used in vocal cord procedures. If a laser penetrates the endotracheal tube and ignites a fire the results can be devastating.[2] The ASA practice advisory recommends that during laser procedures, a laser resistant endotracheal tube (ETT) should be used and chosen for resistance to the laser used for the procedure. It is recommended the ETT cuff(s) be inflated with colored saline in order to be noticed if the laser ruptures the ETT cuff. The surgeon should notify the anesthesiologist in advance of activation of the laser in order for the anesthesiologist to reduce oxygen and allow the oxygen enriched atmosphere to dissipate before activation of the laser.[6]

Fires have also occurred when the trachea is entered with an ESU during tracheostomy. Often patients requiring tracheostomy will have high FiO_2 requirements. It is important that in this instance the trachea is entered with a cold knife or scissors and not an ESU.[6]

Minimizing fuel sources and being careful with them is essential in lowering the risk of surgical fires. Alcohol containing prep solutions should be given several minutes to completely dry before surgical draping is performed in order to allow vapors to disseminate. Care should be taken that the prep is not sloppy such that pools of prep solution accumulate around the patient. These pools take longer to dry and evaporate and thus increase the risk of fire.[9] In an emergency procedure non-alcohol based prep solutions should be used during the surgical prep.

Using moist or wet sponges during high risk procedures is recommended, taking care to insure they do not dry out during the procedure.[6] During head and neck procedures it is suggested to coat exposed hair with a water soluble lubricating jelly to make it nonflammable.[3] Using surgical gowns and drapes that resist combustion is also advised.

The Anesthesia Patient Safety Foundation (APSF) has produced a fire prevention algorithm to assist clinicians in making decisions in cases in which a patient may be at risk for surgical fire.[10] The algorithm recommends room air sedation if the patient is at risk for surgical fire. If oxygen supplementation greater than 30% FiO_2 is required then the recommendation is made to secure the airway with an endotracheal tube or supraglottic airway device.

It is recommended that members of the surgical team discuss the procedure before the case in order to assess the risk of surgical fire. If a procedure is determined to be at high risk then a discussion should be held to determine what steps are being done to prevent a fire occurring and what to do in the event of a fire. The ASA Practice Advisory recommends that every anesthesiologist have knowledge of institutional fire safety protocols for the OR and that they should participate in OR fire safety education. The practice advisory also states that anesthesiologists should participate in OR fire drills with other members of the OR team.[6]

Managing a Patient Fire in the Operating Room

Prevention is the only effective cure for surgical fires. However if a surgical fire occurs, having a prepared and trained team is essential in keeping a serious event from devolving into a potentially catastrophic event. Managing an on-patient fire involves several steps: 1.recognizing early signs of fire, 2. stopping the procedure, 3. taking steps to extinguish the fire, 4. evacuating if necessary, 5. providing post-fire care to the patient.[6]

A fire may be preceded by odors, smoke, a flash or unusual sounds. If these are seen, smelled or heard, then serious attention should be directed to discovering the source and stopping further progression. If a fire occurs, the procedure must be halted immediately. An announcement of fire should be made. The flow of all airway gases

should be stopped. For airway fires, the endotracheal tube should be removed simultaneously with stopping the flow of gases. Pour water into the airway to extinguish burning material. Burning drapes should be removed and thrown on the ground and extinguished. It is important to remember that many surgical drapes are impervious to water and actually repel water. If water is applied to the drapes the fire can continue to burn underneath.[2] Thus the importance of removing the drapes from the patient. Remaining fire should be extinguished with water or saline. If necessary a CO_2 fire extinguisher should be used. If the fire persists after use of the fire extinguisher then activate the fire alarm and evacuate the patient if feasible. Close the door to the room and do not reopen it or enter the room. Shut off the medical gas supply to the room. As can be seen from these steps, having a plan in place will allow the fire to be managed in a stepwise fashion. Having practiced fire drills previously will ensure team members know their roles as well as the location of fire extinguishers and medical gas supply controls.[6]

As quickly as possible the patient should be assessed for burn injury, as well as inhalational injury if they were not intubated at the time of fire. Appropriate steps should be taken to address the patient's injuries. Consideration should be given to intubating the patient if an inhalational injury is suspected. In the case of an airway fire, the patient should be reintubated. Bronchoscopy should be considered to assess the extent of damage.

The event should be reported according to local regulatory requirements. Institutional protocols should be followed in treating the fire as an adverse event. The hospital risk management office should be notified.

As mentioned previously, fire drills are an important component of being prepared to respond if a fire occurs. It is important for members of the OR team to know where fire extinguishers are located and what type of fire extinguisher is present. Fire extinguishers are classified into three basic types according to the types of fire for which they are meant to be used. Class A extinguishers are used on wood, cloth, paper and plastics, Class B extinguishers are used for flammable liquids or grease. Class C extinguishers are used on energized electrical equipment. Many fire extinguishers are classified to be used for two or three types of fires. Carbon dioxide fire extinguishers are recommended for the operating room. They can be used on class B and C fires as well as class A fires. The carbon dioxide gas has liquid and solid components that vaporize which leads to cooling and smothering of the fire. Carbon dioxide extinguishers do not leave a residue and thus do not harm electrical equipment. The cold associated with use of a carbon dioxide extinguisher can cause freezing if it comes into contact with exposed skin.[11]

In using a fire extinguisher, the acronym "PASS" should be remembered. P- Pull the pin to unlock the handle of the extinguisher. A-Aim the nozzle at the base of the fire. S- Squeeze the handle to activate the extinguisher. S- Sweep the stream of the extinguisher over the base of the fire.[2]

Summary

Surgical fires are serious, potentially fatal events. They are preventable. Proper education, training and understanding of the fire triangle should make surgical fires extremely rare events. Participation of the entire surgical team in OR fire safety education and fire drills should enable a quick response and lessen the severity of patient injury should a fire occur.

The Anesthesia Patient Safety Foundation in association with the ECRI Institute has produced an 18 minute video: Prevention and Management of Operating Room Fires. This can be viewed on the APSF website www.apsf.org. A complimentary copy can be ordered on the website.

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Hemorrhagic and Infectious Complications of Neuraxial Anesthesia

Terese T. Horlocker, M.D. **Rochester, Minnesota**

Spinal Hematoma

The actual incidence of neurologic dysfunction resulting from hemorrhagic complications associated with neuraxial blockade is unknown; however, recent epidemiologic studies suggest the incidence is increasing (1). In a review of the literature between 1906 and 1994, Vandermeulen et al. (2) reported 61 cases of spinal hematoma associated with epidural or spinal anesthesia. In 87% of patients, a hemostatic abnormality or traumatic/difficult needle placement was present. More than one risk factor was present in 20 of 61 cases. Importantly, although only 38% of patients had partial or good neurologic recovery, spinal cord ischemia tended to be reversible in patients who underwent laminectomy within eight hours of onset of neurologic dysfunction.

It is impossible to conclusively determine risk factors for the development of spinal hematoma in patients undergoing neuraxial blockade solely through review of the case series, which represent only patients with the complication and do not define those who underwent uneventful neuraxial analgesia. However, large inclusive surveys that evaluate the frequencies of complications (including spinal hematoma), as well as identify subgroups of patients with higher or lower risk, enhance risk stratification. In the series by Moen et al. (3) involving nearly 2 million neuraxial blocks, there were 33 spinal hematomas. The methodology allowed for calculation of frequency of spinal hematoma among patient populations. For example, the risk associated with epidural analgesia in women undergoing childbirth was significantly less (1 in 200,000) than that in elderly women undergoing knee arthroplasty (1 in 3600, $p<0.0001$). Likewise, women undergoing hip fracture surgery under spinal anesthesia had an increased risk of spinal hematoma (1 in 22,000) compared to all patients undergoing spinal anesthesia (1 in 480,000).

Overall, these series suggest that the risk of clinically significant bleeding varies with age (and associated abnormalities of the spinal cord or vertebral column), the presence of an underlying coagulopathy, difficulty during needle placement, and an indwelling neuraxial catheter during sustained anticoagulation (particularly with standard heparin or LMWH). They also consistently demonstrate the need for prompt diagnosis and intervention. Practice guidelines or recommendations summarize evidence-based reviews. However, the rarity of spinal hematoma defies a prospective-randomized study, and there is no current laboratory model. As a result, the *consensus statements* developed by the American Society of Regional Anesthesia and Pain Medicine represent the collective experience of recognized experts in the field of neuraxial anesthesia and anticoagulation (4). They are based on case reports, clinical series, pharmacology, hematology, and risk factors for surgical bleeding. An understanding of the complexity of this issue is essential to patient management.

Oral Anticoagulants

Clinical experience with patients who, congenitally, are deficient in factors II, IX, or X suggests that a factor activity level of 40% for each factor is adequate for normal or near-normal hemostasis. Bleeding may occur if the level of any clotting factor is decreased to 20% to 40% of baseline. The PT is most sensitive to the activities of factors VII and X and is relatively insensitive to factor II. During the first few days of therapy, the PT reflects primarily a reduction of factor VII, the half-life of which is approximately 6 hrs. After a single dose, marked prolongation of the INR may occur, although adequate factor levels are still present. However, with additional doses, an INR greater than 1.4 is typically associated with factor VII activity less that 40% (and the potential for inadequate clotting) (5).

Few data exist regarding the risk of spinal hematoma in patients with indwelling epidural catheters who are anticoagulated with warfarin. The optimal duration of an indwelling catheter and the timing of its removal also remain controversial. Odoom and Sih (6) performed 1000 continuous lumbar epidural anesthetics in vascular surgical patients who were receiving oral anticoagulants *preoperatively*. The thrombotest (a test measuring factor IX activity) was decreased (but not below 10% activity) in all patients prior to needle placement. Heparin was also administered intraoperatively. Epidural catheters remained in place for 48 hours postoperatively. There were no neurologic complications. While these results are reassuring, the obsolescence of the thrombotest as a measure of anticoagulation combined with the unknown coagulation status of the patients at the time of catheter removal limit the usefulness of these results. Therefore, except in extraordinary circumstances, spinal or epidural needle/catheter placement and removal should not be performed in fully anticoagulated patients.

There were no symptomatic spinal hematomas in two smaller series with a total of nearly 700 patients undergoing neuraxial block in combination with warfarin anticoagulation perioperatively (6-8). In both studies, epidural catheters were left indwelling approximately two days. The mean international normalized ratio (INR) at the time of catheter removal was 1.4, although in a small number of patients the INR was therapeutic (2.0-3.0). A large variability in patient response to warfarin was also noted, demonstrating the need for close monitoring of the coagulation status. There were no spinal hematomas in a series of 11,235 patients receiving epidural analgesia after total knee replacement (9). Patients received warfarin (5-10 mg) starting the night of surgery. Epidural catheters were removed within 48 hrs. The mean INR in a subset of 1030 patients at the time of catheter removal was 1.5 (range, 0.9-4.3); the INR was less than 1.5 in nearly 40% of patients. These series suggest that not only the INR but also the duration of warfarin therapy must be considered and that prolongation within the first 48 hrs may represent a significant increase in risk.

Intravenous and Subcutaneous Standard Heparin

The safety of neuraxial techniques in combination with intraoperative heparinization is well documented, providing no other coagulopathy is present. In a study involving over 4000 patients, Rao and El-Etr (10) demonstrated the safety of indwelling spinal and epidural catheters during systemic heparinization during vascular surgery. However, the heparin was administered at least 60 minutes after catheter placement, level of anticoagulation was closely monitored, and the indwelling catheters were removed at a time when circulating heparin levels were relatively low. A subsequent study in the neurologic literature by Ruff and Dougherty (11) reported spinal hematomas in 7 of 342 patients (2%) who underwent a diagnostic lumbar puncture and subsequent heparinization. Traumatic needle placement, initiation of anticoagulation within one hour of lumbar puncture and concomitant aspirin therapy were identified as risk factors in the development of spinal hematoma in anticoagulated patients. Subsequent studies using similar methodology have verified the safety of this practice, provided the monitoring of anticoagulant effect and the time intervals between heparinization and catheter placement/removal are maintained.

Low-dose subcutaneous standard (unfractionated) heparin is administered for thromboprophylaxis in patients undergoing major thoracoabdominal surgery and in patients at increased risk of hemorrhage with oral anticoagulant or low molecular weight heparin (LMWH) therapy. There are nine published series totaling over 9,000 patients who have received this therapy without complications(12), as well as extensive experience in both Europe and United States without a significant frequency of complications. There are only five case reports of neuraxial hematomas, four epidural (2,13) and one subarachnoid,(14) during neuraxial block with the use of subcutaneous heparin.

The largest study of thrice daily unfractionated heparin involved 768 epidural catheter placements. Sixteen patients from this group had a positive match for hemorrhage codes on their discharge records, with none of the episodes being identified within a major hemorrhage category. Laboratory value analysis failed to reveal changes in the aPTT values of significance (4). The safety of neuraxial blockade in patients receiving doses greater than 10,000 U of UFH daily or more than twice-daily dosing of UFH has not been established. Although the use of thrice-daily UFH may lead to an increased risk of surgical-related bleeding, it is unclear whether there is an increased risk of spinal hematoma. If thrice-daily unfractionated heparin is administered, techniques to facilitate detection of new/progressive neurodeficits (eg, enhanced neurologic monitoring occur and neuraxial solutions to minimize sensory and motor block) should be applied.

Low Molecular Weight Heparin

Extensive clinical testing and utilization of LMWH in Europe over the last ten years suggested that there was not an increased risk of spinal hematoma in patients undergoing neuraxial anesthesia while receiving LMWH thromboprophylaxis perioperatively (2,15). However, in the five years since the release of LMWH for general use in the United States in May 1993, over 60 cases of spinal hematoma associated with neuraxial anesthesia administered in the presence of perioperative LMWH prophylaxis were reported to the manufacturer (16,17). Many of these events occurred when LMWH was administered intraoperatively or early postoperatively to patients undergoing continuous epidural anesthesia and analgesia. Concomitant antiplatelet therapy was present in several cases. The apparent difference in incidence in Europe compared to the United States may be a result of a difference in dose and dosage schedule. For example, in Europe the recommended dose of enoxaparin is 40 mg once daily (with LMWH therapy initiated 12 hours preoperatively), rather than 30 mg every twelve hours. However, timing of catheter removal may also have an impact. It is likely that the lack of a trough in anticoagulant activity associated with twice daily dosing resulted in catheter removal occurring during significant anticoagulant activity. Importantly, there are no data to suggest that the risk of spinal hematoma is increased with specific LMWH formulations (16). The incidence of spinal hematoma in patients undergoing neuraxial block in combination with LMWH has been estimated at 1 in 40,800 spinal anesthetics and 1 in 3100 continuous epidural anesthetics (18). It is interesting in that the frequency of spinal hematoma in this series is similar to that reported by Moen et al (3) for women undergoing total knee replacement with epidural analgesia.

Indications for thromboprophylaxis as well as treatment of thromboembolism or MI have been introduced. These new applications and corresponding regional anesthetic management warrant discussion (19). Several off-label applications of LMWH are of special interest to the anesthesiologist. LMWH has been demonstrated to be efficacious as a “bridge therapy” for patients chronically anticoagulated with warfarin, including parturients, patients with prosthetic cardiac valves, a history of atrial fibrillation, or preexisting hypercoagulable condition. The doses of LMWH are those associated with DVT treatment, not prophylaxis, and are much higher. An interval of at least 24 hours is required for the anticoagulant activity to resolve.

Dabigatran

Dabigatran etexilate is a prodrug that specifically and reversibly inhibits both free and clot-bound thrombin. The drug is absorbed from the gastrointestinal tract with a bioavailability of 5%(20). Once absorbed it is converted by esterases into its active metabolite, dabigatran. Plasma levels peak at two hours. The half-life is eight hours after a single dose and up to 17 hours after multiple doses. It is likely that once daily dosing will be possible for some indications because of the prolonged half-life. Because 80% of the drug is excreted unchanged by the kidneys, it is contraindicated in patients with renal failure(21). Dabigatran prolongs the aPTT, but its effect is not linear and reaches a plateau at higher doses. However, the ecarin clotting time (ECT) and thrombin time (TT) are particularly sensitive and display a linear dose response at therapeutic concentrations. Reversal of anticoagulant effect is theoretically possible through administration of recombinant factor VIIa, although this has not been attempted

clinically(21). Indeed, product labeling suggests that dialysis may be considered for patients with significant bleeding due to dabigatran.

Rivaroxaban

Rivaroxaban is a potent selective and reversible oral activated factor Xa inhibitor, with an oral bioavailability of 80%. After administration, the maximum inhibitory effect occurs one to four hours, however, inhibition is maintained for 12 hours. The antithrombotic effect can be monitored with the PT, aPTT and Heptest, all of which demonstrate linear dose effects. Rivaroxaban is cleared by the kidneys and gut. The terminal elimination half-life is nine hours in healthy volunteers and may be prolonged to 13 hours in the elderly due to a decline in renal function (hence a need for dose adjustment in patients with renal insufficiency and contraindicated in patients with severe liver disease).

Rivaroxaban was approved in the United States for thromboprophylaxis following total hip or knee replacement in 2011. Overall, clinical trials comparing rivaroxaban (5- 40mg mg daily, with the first dose six to eight hours after surgery) with enoxaparin (40 mg, beginning 12 hours before surgery) demonstrate similar rates of bleeding and comparable efficacy. While a "regional anesthetic" was performed in over half of the patients included in the clinical trials, no information regarding needle placement or catheter management was included. Although there have been no reported spinal hematomas, the lack of information regarding the specifics of block performance and the prolonged half-life warrants a cautious approach.

A minimum of three days should elapse between discontinuation of rivaroxaban and neuraxial block. Indwelling neuraxial catheters are contraindicated due to the "boxed warning". Likewise, indwelling neuraxial catheters should be removed six hours prior to initiation of rivaroxaban therapy postoperatively.

Apixaban

Apixaban inhibits platelet activation and fibrin clot formation via direct, selective and reversible inhibition of free and clot-bound factor Xa. , The oral bioavailability is 50%. After administration, the maximum inhibitory effect occurs in three to four hours, however, inhibition is maintained for 12 hours. Apixaban is cleared by the liver and kidneys. The terminal elimination half-life is 12 hours in healthy volunteers and may be prolonged in patients with renal impairment.

A minimum of three days should elapse between discontinuation of apixaban and neuraxial block. Indwelling neuraxial catheters are contraindicated and should be removed six hours prior to initiation of rivaroxaban therapy postoperatively.

Table 1 Recommendations for Management of Patients Receiving Neuraxial Blockade and Anticoagulant Drugs

Warfarin	Discontinue chronic warfarin therapy 4–5 days before spinal procedure and evaluate INR. INR should be within the normal range at time of procedure to ensure adequate levels of all vitamin K-dependent factors. Postoperatively, daily INR assessment with catheter removal ideallyoccurring with INR< 1.5; monitor carefully for 1.5 < INR < 3.0
Antiplatelet medications	No contraindications with aspirin or other NSAIDs. Thienopyridine derivatives should be discontinued to allow complete recovery of platelet function (clopidogrel 5-7 days, ticlodipine 10 days, prasugrel 7-10 days, and ticagrelor 5-7 days) prior to procedure. GP IIb/IIIa inhibitors should be discontinued to allow recovery of platelet function prior to procedure (8 hours for tirofiban and eptifibatide, 24–48 hours for abciximab).
Thrombolytics/ fibrinolytics	There are no available data to suggest a safe interval between procedure and initiation or discontinuation of these medications. Follow fibrinogen level and observe for signs of neural compression.
LMWH	Delay procedure at least 12 hours from the last dose of thromboprophylaxis LMWH dose. For "treatment" dosing of LMWH, at least 24 hours should elapse prior to procedure. LMWH should not be administered within 24 hours after the procedure. Indwelling epidural catheters should be maintained only with once daily dosing of LMWH and strict avoidance of additional haemostasis altering medications, including NSAIDs. Post catheter removal, wait 4 hrs for subsequent LMWH dose.
Unfractionated SQ heparin	Delay needle/catheter placement 4-6 hours after last dose or document normal aPTT For higher dosing regimens, longer delays are needed. Also increase neurologic monitoring and cautiously co-administer antiplatelet medications.
Unfractionated IV heparin	Delay needle/catheter placement 2-4 hours after last dose, document normal aPTT. Heparin may be restarted 1 hour following procedure. Sustained heparinization with an indwelling neuraxial catheter associated with increased risk; monitor neurologic status aggressively.
Dabigatran	Discontinue 5 days prior to procedure; for shorter time periods, document normal TT. First postoperative dose 24 h after needle placement and 6 hours post catheter removal (whichever is later).
Rivaroxaban, Apixaban, and Edoxaban	Discontinue 3 days prior to procedure. First postoperative dose 24 h after needle placement and 6 hours post catheter removal (whichever is later).

Antiplatelet Medications

Antiplatelet medications are seldom used as primary agents of thromboprophylaxis. However, many orthopedic patients report chronic use of one or more antiplatelet drugs. Although Vandermeulen et al (2) implicated antiplatelet therapy in 3 of the 61 cases of spinal hematoma occurring after spinal or epidural anesthesia, several large studies have demonstrated the relative safety of neuraxial blockade in both obstetric, surgical and pain clinic patients receiving these medications (22-24). In a prospective study involving 1000 patients, Horlocker et al (24) reported that preoperative antiplatelet therapy did not increase the incidence

of blood present at the time of needle/catheter placement *or* removal, suggesting that trauma incurred during needle or catheter placement is neither increased nor sustained by these medications. The clinician should be aware of the possible increased risk of spinal hematoma in patients receiving antiplatelet medications who undergo subsequent heparinization (11). Ticlopidine and clopidogrel are also platelet aggregation inhibitors. These agents interfere with platelet-fibrinogen binding and subsequent platelet-platelet interactions. The effect is irreversible for the life of the platelet. Platelet dysfunction is present for 5-7 days after discontinuation of clopidogrel and 10-14 days with ticlopidine.

Prasugrel is a new thienopyridine that inhibits platelets more rapidly, more consistently, and to a greater extent than do standard and higher doses of clopidogrel. In the United States, the only labeled indication is for acute coronary syndrome in patients intended to undergo percutaneous coronary intervention. After a single oral dose, 50% of platelets are irreversibly inhibited, with maximum effect two hours after administration. Platelet aggregation normalizes in 7-9 days after discontinuation of therapy. The labeling recommends that the drug "be discontinued at least 7 days prior to any surgery". Platelet glycoprotein IIb/IIIa receptor antagonists, including abciximab (Reopro ®), eptifibatide (Integrilin ®) and tirofiban (Aggrastat ®), inhibit platelet aggregation by interfering with platelet-fibrinogen binding and subsequent platelet-platelet interactions. Time to normal platelet aggregation following discontinuation of therapy ranges from eight hours (eptifibatide, tirofiban) to 48 hours (abciximab). Increased perioperative bleeding in patients undergoing cardiac and vascular surgery after receiving ticlopidine, clopidogrel and glycoprotein IIb/IIIa antagonists warrants concern regarding the risk of anesthesia-related hemorrhagic complications.

Anesthetic Management of the Anticoagulated Patient

The decision to perform spinal or epidural anesthesia/analgesia and the timing of catheter removal in a patient receiving thromboprophylaxis should be made on an individual basis, weighing the small, though definite risk of spinal hematoma with the benefits of regional anesthesia for a specific patient. Alternative anesthetic and analgesic techniques exist for patients considered to be at an unacceptable risk. The patient's coagulation status should be optimized at the time of spinal or epidural needle/catheter placement, and the level of anticoagulation must be carefully monitored during the period of epidural catheterization (Table 1). It is important to note that patients respond with variable sensitivities to anticoagulant medications. Indwelling catheters should not be removed in the presence of a significant coagulopathy, as this appears to significantly increase the risk of spinal hematoma (2,3). In addition, communication between clinicians involved in the perioperative management of patients receiving anticoagulants for thromboprophylaxis is essential in order to decrease the risk of serious hemorrhagic complications. The patient should be closely monitored in the perioperative period for signs of cord ischemia. If spinal hematoma is suspected, the treatment of choice is immediate decompressive laminectomy. Recovery is unlikely if surgery is postponed for more than 10-12 hours; less than 40% of the patients in the series by Vandermeulen et al. (2) had partial or good recovery of neurologic function.

Meningitis and Epidural Abscess

Bacterial infection of the central neuraxis may present as meningitis or cord compression secondary to abscess formation. Possible risk factors include underlying sepsis, diabetes, depressed immune status, steroid therapy, localized bacterial colonization or infection, and chronic catheter maintenance. Bacterial infection of the central neural axis may present as meningitis or cord compression secondary to abscess formation. The infectious source for meningitis and epidural abscess may result from distant colonization or localized infection with subsequent hematogenous spread and CNS invasion. The anesthetist may also transmit microorganisms *directly* into the CNS by needle/catheter contamination through a break in aseptic technique or passage through a contiguous infection. An indwelling neuraxial catheter, though aseptically sited, may be colonized with skin flora and consequently serve as a source for ascending infection to the epidural or intrathecal space.

Historically, the frequency of serious CNS infections such as arachnoiditis, meningitis, and abscess following spinal or epidural anesthesia was considered to be extremely low- cases were reported as individual cases or small series (25,26). However, recent epidemiologic series from Europe suggest that the frequency of infectious complications associated with neuraxial techniques is increasing (3,27). In a national study conducted from 1997 to 1998 in Denmark, Wang et al (28) reported the incidence of epidural abscess after epidural analgesia was 1:1930 catheters. Patients with epidural abscess had an extended duration of epidural catheterization (median 6 days, range 3-31 days). In addition, the majority of the patients with epidural abscess were immunocompromised. Often the diagnosis was delayed; the time to first symptom to confirmation of the diagnosis was a median of five days. *S. aureus* was isolated in 67% of patients. Patients without neurologic deficits were successfully treated with antibiotics, while those with deficits underwent surgical decompression, typically with only moderate neurologic recovery. It is difficult to determine why the frequency of symptomatic epidural abscess was so high in this series. Since perioperative antithrombotic therapy was involved in most cases, it is possible that the epidural abscesses were infected "micro" epidural hematomas, but this is not strongly supported by the diagnostic imaging studies and neurosurgical findings.

In the series by Moen et al (3) there were 42 serious infectious complications. Epidural abscess occurred in 13 patients; nine (70%) were considered immunocompromised as a result of diabetes, steroid therapy, cancer or alcoholism. Six patients underwent epidural block for analgesia following trauma. The time from placement of the epidural catheter to first symptoms ranged from 2 days to 5 weeks (median 5 days). Although prevailing symptoms were fever and sever backache, five developed neurologic deficits. All seven positive cultures isolated *S. aureus*. Overall neurologic recovery was complete in 7 of 12 patients. However, four of the five patients with neurologic symptoms did not recover. Meningitis was reported in 29 patients for an overall

incidence of 1:53,000. A documented perforation of the dura (intentional or accidental) occurred in 25 of 29 cases. In the 12 patients in whom positive cultures were obtained, alpha-hemolytic streptococci were isolated in 11 patients and *S. aureus* in one.

These large epidemiologic studies represent new and unexpected findings regarding the demographics, frequency, etiology and prognosis of infectious complications following neuraxial anesthesia. Epidural abscess is most likely to occur in immunocompromised patients with prolonged durations of epidural catheterization. The most common causative organism is *S. aureus*, which suggests the colonization and subsequent infection from normal skin flora as the pathogenesis. Delays in diagnosis and treatment result in poor neurologic recovery, despite surgical decompression. Conversely, patients who develop meningitis following neuraxial blockade typically are healthy and have undergone uneventful spinal anesthesia. Furthermore, the series by Moen et al (3) validates the findings of individual case reports of meningitis after spinal anesthesia- the source of the pathogen is mostly likely to be the upper airway of the proceduralist. While the frequency of serious infectious complications is much higher than reported previously, the results may be due to differences in reporting and/or clinical practice (asepsis, perioperative antibiotic therapy, duration of epidural catheterization)

Meningitis after Dural Puncture and Neuraxial Anesthesia

Dural puncture has long been considered a risk factor in the pathogenesis of meningitis. Exactly how bacteria cross from the blood stream into the spinal fluid is unknown. The presumed mechanisms include introduction of blood into the intrathecal space during needle placement and disruption of the protection provided by the blood-brain barrier. Initial investigations were performed over 80 years ago (29). Subsequent clinical studies reported conflicting results regarding the causal relationship between dural puncture during bacteremia and meningitis However, the protective effect of antibiotic administration prior to lumbar puncture was suggested (30,31).

Epidural Abscess after Epidural Anesthesia

Several relevant studies have specifically examined the risk of epidural abscess in patients receiving epidural anesthesia and/or analgesia. Bader et al. (32) investigated the use of regional anesthesia in women with chorioamnionitis. Three hundred nineteen women were identified from a total of 10,047 deliveries. Of the 319 women, 100 had blood cultures taken on the day of delivery. Eight of these had blood cultures consistent with bacteremia. Two hundred ninety-three of the 319 patients received a regional anesthetic, in 43 patients antibiotics were administered prior to needle or catheter placement. No patient in the study, including those with documented bacteremias, had infectious complications. In addition, mean temperatures and leukocyte counts in patients who received blood cultures showed no significant differences between bacteremic and nonbacteremic groups. These authors continue to administer spinal and epidural anesthesia in patients with suspected chorioamnionitis because the potential benefits of regional anesthesia outweigh the theoretical risk of infectious complications.

The safety of epidural analgesia in 75 patients admitted to the intensive care unit was prospectively evaluated by Darchy et al (33). There were no epidural abscesses. However, five of nine patients with positive cultures of the catheter insertion site also had positive catheter tip cultures (epidural catheter infection); *Staphylococcus epidermidis* was the most commonly cultured microorganism. Local infection of the catheter site was treated with catheter removal, but antibiotic therapy was not specifically prescribed. Concomitant infection at other sites, antibiotic prophylaxis, and duration of epidural analgesia were not risk factors for epidural-analgesia related infections. The authors noted that the presence of both erythema and local discharge is a strong predictor of local and epidural catheter infection.

Epidural anesthesia and analgesia in a patient with a known systemic or localized infection remains controversial. Jakobsen et al (34) retrospectively reviewed the records of 69 patients with abscesses or wound infections who underwent epidural catheter placement for surgical debridement over a seven year-period. Several patients had more than one catheter inserted. Catheters were left indwelling for a mean of nine days. On 12 occasions (eight patients) the catheter was removed because of local infection. None of the patients demonstrated signs or symptoms of neuraxial infection. The authors concluded that epidural anesthesia is relatively safe for patients requiring repeated surgical treatment of localized infection. In contrast, Bengtsson et al. (35) reported three epidural catheter-related infections in patients with cutaneous wounds over a four year-period. All patients were treated with antibiotic therapy; one patient underwent transcutaneous drainage of an epidural abscess. However, there were no neurologic deficits. It is difficult to determine the actual risk of epidural abscess in patients with chronic localized infections who undergo epidural catheter placement due to the small number of patients studied and the rarity of this complication. Therefore, the clinician must maintain vigilance in neurologic monitoring to assure early recognition and treatment.

Neuraxial Blockade in the Immunocompromised Patient

Large series have demonstrated that patients with immunodeficiencies are at increased risk for infectious complications compared to those with intact immune function. However, there are few investigations which have evaluated the frequency of meningitis or epidural abscess within a specific immunodeficient population (3,27,36).

Table 2. Infectious Complications following Neuraxial Anesthesia in the Immunocompromised Patient

- The attenuated inflammatory response within the immunocompromised patient may diminish the clinical signs and symptoms often associated with infection and result in a delay in diagnosis and treatment.
- The range of microorganisms causing invasive infection in the immunocompromised host is much broader than that affecting the general population and includes atypical and opportunistic pathogens.
- Early and effective therapy is paramount in optimizing neurologic outcome- consultation with an infectious disease specialist is advised.
- Prolonged antibiotic therapy (weeks-months) is often required because of persistent and immunologic deficiencies.
- Since eradication of infection is difficult once established, prevention of infection is paramount in caring for immunocompromised patients.

From: Horlocker, et al 2006, with permission

Herpes Simplex Virus

Herpes simplex virus type 2 (HSV-2) infection is an incurable, recurrent disease characterized by asymptomatic periods alternating with recrudescence of genital lesions. The primary infection is associated with viremia and can be accompanied by a variety of symptoms, including fever, headache, and rarely aseptic meningitis. In contrast, recurrent or secondary infections present as genital lesions without evidence of viremia. When obstetric patients present for delivery with evidence of active HSV-2 infection, cesarean section is recommended to avoid exposing the neonate to the virus during vaginal delivery. Neuraxial block in these patients is controversial because of the theoretical potential of introducing the virus into the CNS. However, there are little data to support these concerns.

Human Immunodeficiency Virus

The risk of performing neuraxial block in patients infected with human immunodeficiency virus (HIV) is largely undetermined. Approximately 40% of patients with the diagnosis of acquired immune deficiency syndrome (AIDS) have clinical signs of neuropathy, and 70% to 80% have neuropathic changes present at autopsy. Since the virus infects the CNS early in the disease, it is unlikely that neuraxial block would result in new CNS transmission. However, the neurologic symptoms associated with HIV infection such as aseptic meningitis, headache, and polyneuropathy would be indistinguishable from those related to regional technique. Hughes et al. (37) reported safe administration of neuraxial block to 18 HIV-infected parturients. The patients studied showed no postpartum change in immune, infectious or neurologic status. Avidan et al. (38) and Bremerich et al.(39) also reported a low complication rate for parturients with HIV infection on antiretroviral therapy who underwent spinal anesthesia. However, in all three series (with a combined total of 117 patients), the patients were relatively healthy and in the early stage of their disease. The effects of anesthesia on patients with more advanced disease are unreported.

Aseptic Technique

Although previous publications have repeatedly recommended meticulous aseptic technique, only recently have standards for asepsis during the performance of regional anesthetic procedures been defined (40) (Table 3). *Handwashing* remains the most crucial component of asepsis; gloves should be regarded as a supplement to- not a replacement of- handwashing (41). The use of an antimicrobial soap reduces bacterial growth and reduces the risk of bacteria being released into the operative field should gloves become torn or punctured during the procedure. An alcohol-based antiseptic provides the maximum degree of antimicrobial activity and duration. Prior to washing, all jewelry (rings, watches, etc) should be removed; higher microbial counts have been noted in health care workers who do not routinely remove these items before handwashing. *Sterile gloves* protect not only patients from contamination, but also health care workers from blood-borne pathogens and are required by the Occupational Safety and Health Administration (40). Glove leaks are more likely to occur with vinyl compared to latex gloves (24% vs. 2), with contamination of the health care workers' hands noted following the leaks in 23% of cases (42). Conversely, the use of *gowns* does not further reduce the likelihood of cross contamination in an intensive care unit setting compared to gloves alone. At this time, there are insufficient data to make recommendations regarding routine use for single injection or temporary neuraxial/peripheral catheter placement. However, placement of an *indwelling* permanent device, such as a spinal cord stimulator, warrants the same asepsis as a surgical procedure, including gowns, hats, and antibiotic pretreatment (40,43).

Surgical *masks*, initially considered a barrier to protect the proceduralist from patient secretions and blood, are now required by the Center for Disease Control due to the increasing number of cases of post spinal meningitis, many of which result from contamination of the epidural or intrathecal space with pathogens from the operator's buccal mucosa (3,44-47). A recent ASA Practice Advisory also recommends the wearing of masks (48).

Antiseptic Solutions

Controversy still exists regarding the most appropriate and safe antiseptic solution for patients undergoing neuraxial and peripheral techniques. Povidone iodine and chlorhexidine gluconate (with or without the addition of isopropyl alcohol) have been most extensively studied (49,50). In nearly all clinical investigations, the bactericidal effect of chlorhexidine was more rapid and more effective (extending its effect hours following its application) than povidone iodine. The addition of isopropyl alcohol accelerates these effects. Chlorhexidine is effective against nearly all nosocomial yeasts, and bacteria (gram-positive and gram-

negative); resistance is extremely rare. It also remains effective in the presence of organic compounds, such as blood. It must be noted that chlorhexidine-alcohol labeling contains a warning against use as a skin preparation prior to lumbar puncture. The FDA has not formally approved chlorhexidine for skin preparation prior to lumbar puncture because of the lack of animal and clinical studies examining the neurotoxic potential of chlorhexidine, *not* due to a number of reported cases of nerve injury. Indeed, it is important to note that there are no cases of neurotoxicity with *either* chlorhexidine or alcohol (40). Therefore, as a result of its superior effect, alcohol-based chlorhexidine solutions are considered the antiseptic of choice for skin preparation before any regional anesthetic procedure (40).

Anesthetic Management of the Infected or Febrile Patient

In summary, several clinical and laboratory studies have suggested an association between dural puncture during bacteremia and meningitis. The data are not equivocal, however. The clinical studies are limited to pediatric patients who are historically at high-risk for meningitis. Many of the original animal studies utilized bacterial counts that were far in excess of those noted in humans in early sepsis, making CNS contamination more likely. Despite these conflicting results, it is generally recommended that except in the most extraordinary circumstances, central neuronal block should not be performed in patients with untreated bacteremia. Patients with evidence of systemic infection may safely undergo spinal anesthesia, if antibiotic therapy is initiated *prior* to dural puncture, and the patient has demonstrated a response to therapy, such as a decrease in fever. Placement of an indwelling epidural (or intrathecal) catheter in this group of patients remains controversial; patients should be carefully selected and monitored for evidence of epidural infection (51).

The attenuated inflammatory response within the immunocompromised patient, including patients with HSV and HIV, may diminish the clinical signs and symptoms often associated with infection. Likewise, the range of microorganisms causing invasive infection in the immunocompromised host is much broader than that affecting the general population and includes atypical and opportunistic pathogens. Consultation with an infectious disease specialist is advised to facilitate initiation of early and effective therapy (36). Meticulous aseptic technique, including hand-washing with chlorhexidine, wearing of mask and sterile gloves by the proceduralist, skin asepsis with chlorhexidine and antibiotic pretreatment for the placement of permanent devices, is critical to the prevention of infectious complications related to regional anesthesia (40).

Table 3. Variables That May Influence Infectious Complications

Site of catheter placement (thoracic vs. lumbar vs. caudal)
Choice of antiseptic and technique of application
Choice of barrier protection (masks, gloves, gowns)
Timing and selection of perioperative antibiotics
Duration of neuraxial or peripheral catheterization
Use of bacterial filters
Dressing type(s) (transparent vs. dry gauze dressing; use of antiseptic dressings)

From: Hebl 2006, with permission

All patients with an established local or systemic infection should be considered at risk for developing infection of the CNS. A delay in diagnosis and treatment of even a few hours significantly worsens neurologic outcome. Bacterial meningitis is a medical emergency. Mortality is approximately 30%, even with antibiotic therapy. The clinical course of epidural abscess progresses from spinal ache and root pain, to weakness (including bowel and bladder symptoms) and eventually paralysis. The initial back pain and radicular symptoms may remain stable for hours to weeks. However, the onset of weakness often progresses to complete paralysis within 24 hours. Although the diagnosis was historically made with myelogram, radiologic examination such as CT scan, or more preferably MRI, is currently recommended. A combination of antibiotics and surgical drainage remains the treatment of choice. As with spinal hematoma, neurologic recovery is dependent on the duration of the deficit and the severity of neurologic impairment before treatment.

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A Mother's Broken Heart: Obstetric Anesthesia in Heart Disease

Katherine W. Arendt, M.D. **Rochester, Minnesota**

Introduction:

In the developed world, cardiac disease is now the leading cause of maternal mortality.[1,2,3] Myocardial infarction, aortic dissection and cardiomyopathy account for a large portion of cardiac maternal death.[4] Congenital heart disease (CHD) in pregnancy is becoming increasingly common,[5] likely because advancements in medical and surgical care have allowed women with CHD to reach child-bearing age. Acquired heart disease (AHD) amongst pregnant women is also growing. This is likely because of increasing maternal age, increasing rates of obesity, and advanced reproductive technologies resulting in older and less-healthy women becoming pregnant. As a result, more women with chronic hypertension, acquired coronary artery disease, aortopathies, and cardiomyopathies are becoming pregnant and presenting to our labor and delivery units.

The anesthetic management of women with CHD and AHD in labor and delivery is complex. Each case should be individualized because each patient's cardiac, obstetric and anesthetic history is unique. For high-risk cardiac patients, multidisciplinary management is paramount and should include obstetrics, cardiology, anesthesiology and neonatology. In planning an obstetric anesthetic for a parturient with cardiac disease it is important to understand the patient's cardiovascular anatomy and hemodynamic physiology, the physiologic changes of pregnancy labor and delivery, the obstetric plan for her delivery, the hemodynamic alterations our anesthetic techniques induce, and what, if any, cardiac or obstetric complications for which she may be at particularly high risk.

Cardiovascular Changes during Pregnancy

The normal cardiovascular changes that occur during pregnancy are listed in Table 1. Systemic vascular resistance and blood pressure decrease while plasma volume and cardiac output (CO) increase during pregnancy. During labor and delivery, CO increases significantly and peaks immediately after birth from contraction of the evacuated uterus resulting in aorto-caval decompression and auto-transfusion of uterine blood into the venous system. The CO at this moment has been documented to be 80% greater than pre-labor values which are already 30-50% greater than pre-pregnancy values.[6]

Table 1. **Normal Cardiovascular Changes During Pregnancy**

Variable	Direction of Change	Average Change
Blood volume	↑	+35%
Plasma volume	↑	+45%
Red blood cell volume	↑	+20%
Cardiac output	↑	+40%
Stroke volume	↑	+30%
Heart rate	↑	+15%
Femoral venous pressure	↑	+15 mm Hg
Total peripheral resistance	↓	–15%
Mean arterial blood pressure	↓	–15 mm Hg
Systolic blood pressure	↓	–0–15 mm Hg
Diastolic blood pressure	↓	–10–20 mm Hg
Central venous pressure	↔	No change

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Planning and Risk Stratification of Parturients with Heart Disease

An anesthesiology consultation should occur in advance of delivery in patients with cardiac disease with particular attention to functional status, intra-cardiac shunting and cyanosis, prior arrhythmias or a current pacemaker or defibrillator, left heart obstructive lesions, prior episodes of heart failure, and left and right heart function. Because severe morbidity and mortality during pregnancy, labor and delivery is more common in patients with preexisting heart disease,[7] it is important that these patients deliver at tertiary and quaternary care centers. Predicting which cardiac parturients may do poorly helps the anesthesiologist in planning location for delivery as well as planning monitoring and anesthetic techniques.

Although various risk stratification systems have been published, [8,9,10] an understanding of the normal cardiovascular adaptations to pregnancy can predict which patients may decompensate in the antepartum or in labor and delivery, and which ones are at lower risk for complications. For example, patients with stenotic aortic valvular lesions are at higher risk of pregnancy-related heart failure than those with insufficient aortic valvular lesions because as the systemic vascular resistance decreases with pregnancy, the decreased afterload deleteriously results in lesser coronary perfusion in aortic stenosis, but beneficially reduces the regurgitant volume in aortic insufficiency. The following lesions in Table 2 and 3 are considered high risk in pregnancy by the American Heart Association, the American College of Cardiology and the European Society of Cardiology.[11,12] It is imperative that these patients deliver at a tertiary/quaternary care center that can care for their cardiac as well as obstetric needs.

Table 2. **High Risk CHD in Pregnancy**
Severe Pulmonary arterial hypertension
Cyanotic CHD
Fontan circulation
Complex CHD complicated by CHF, valvular disease or the need for anticoagulation
CHD with history of malignant arrhythmias
Marfan Syndrome

Table 3. **High Risk Valvular Disease in Pregnancy**
Severe aortic stenosis with or without symptoms
Mitral stenosis with NYHA class II – IV symptoms
Aortic or mitral regurgitation with NYHA class III to IV symptoms
Aortic or mitral valve disease with severe LV dysfunction (EF < 40%)
Aortic or mitral valve disease severe pulmonary hypertension (PA pressure >75 percent of systemic pressure)
Mechanical prosthetic valve

Once the anesthesiologist determines the risk of the patient's cardiac condition in pregnancy, an anesthetic plan can be formulated by combining the predicted physiologic consequences associated with the patient's cardiac lesion, the physiologic changes associated with pregnancy, labor, and delivery, and the hemodynamic alterations induced by different analgesic and anesthetic techniques.

Obstetric Management of Parturients with Heart Disease

Typically, cardiac disease is not an indication for cesarean delivery. Exceptions may include patients with aortic dissection, aortic dilation of > 4.5cm, patient anticoagulated with warfarin at the time of delivery, patients with severe pulmonary hypertension or patients who are in distress requiring intubation or vasopressor administration. Many obstetricians perform a "cardiac delivery" for laboring parturients with significant heart disease. Such a delivery involves an early, dense epidural followed by a passive second stage (no pushing) and a forceps or vacuum delivery. With this technique, catecholamine release is limited by excellent pain control, and hemodynamic fluctuations from maternal expulsive efforts are avoided. However, the risks of a surgical vaginal delivery to both the parturient (e.g. trauma, bleeding) and the neonate (e.g. head injury) need to be weighed against the potential hemodynamic compromise of maternal expulsive efforts.

Labor Analgesia and Monitoring

A "cardiac delivery" with a passive second stage involves an excellent epidural and an involved anesthesia team. In this technique, after uterine contractions bring the fetus to the pelvic floor, low or outlet forceps or vacuum is used to avoid maternal Valsalva. However, even if pushing during second stage is planned, neuraxial analgesia is important in the cardiac parturient for it reduces catecholamine surges from labor pain which can result in tachycardia, hypertension, increased cardiac output, and ventricular stress. Maintaining a dense epidural not only decreases such cardiac stress but it also decreases the degree of hemodynamic alteration should an urgent cesarean delivery be required and the epidural need to be converted to a surgical block quickly.

Pulse oximetry in laboring women is often incorporated in the tocodynonometer machine and provides neither a visible waveform nor audible tones. Laboring women with heart disease should have a pulse oximeter with

a waveform for assessment and audible alarms. If the patient has a history of a tachyarrhythmia, ischemic heart disease, aortic stenosis or hypertrophic cardiomyopathy, then 5-lead ECG telemetry should be utilized during labor and delivery. Specialized nursing in labor and delivery may need to be arranged to interpret telemetric monitoring. Occasionally, an arterial line could be placed for labor management. Rarely would a central line or pulmonary artery catheter be necessary during labor.

The physiologic implications of pregnancy and the anesthetic goals for some common valvular and CHD lesions are reviewed in Table 4. This is not a complete list of all possible cardiac lesions, and many with CHD have multiple different lesions that have been repaired with various techniques resulting in complex hemodynamic physiology. In contrast, patients that have had complete repairs, for example, repaired tetralogy of Fallot with little residual hemodynamic defect, can have few physiologic concerns. However, experts in CHD emphasize that a "repair" is not a "cure" or complete "correction," and therefore patients with CHD, even with good repairs, should be followed by a CHD specialist and have their labor and delivery occur at tertiary centers if possible.

Table 4. **Anesthetic Considerations for Valvular & Shunt Lesions in Pregnancy**

	Physiologic Effects of Pregnancy	**Anesthetic Goals**
Mitral Stenosis	(-) Because of relatively fixed preload to the left ventricle, the heart may not be able to generate increased cardiac output necessary for pregnancy. (-)The increase in blood volume increases left atrial pressure and may lead to atrial fibrillation or pulmonary edema.	-Avoid sinus tachycardia: this allows less time for ventricular filling during diastole. -Avoid atrial fibrillation: loss of atrial contraction can result in failure. In Afib, cardioversion should be considered if drug therapy fails to decrease ventricular rate. -Avoid increases in excess fluids: may precipitate pulmonary edema.
Aortic Stenosis	(-)The decreased SVR can result in lesser coronary perfusion pressure to the thickened LV myocardium.	-Avoid decreases in SVR (neuraxial anesthesia should be titrated carefully) -Avoid hypovolemia, bradycardia or tachycardia.
Mitral / Aortic Insufficiency	(+)The decreased SVR results in a lesser regurgitant volume.	-Avoid increases in SVR and decreases in contractility. Avoid bradycardia. -Maintain sinus rhythm. -Consider afterload reduction (neuraxial anesthesia is generally tolerated well)
R to L Shunt (e.g. TOF, Eisenmenger's, CCHD)	(-)The decrease in SVR increases the right-to-left shunting and possible cyanosis. (+)In unrepaired TOF, the increase in blood volume is beneficial because adequate right ventricular preload is necessary to eject blood past the outflow obstruction and increase pulmonary blood flow. *CCHD, Eisenmenger's and all pulmonary vascular hypertensive diseases, carry a high mortality rate in pregnancy, labor, delivery and the postpartum. Pregnancy implications and anesthetic management is beyond this table.	-Avoid decreases in SVR, which can lead to episodes of cyanosis. Cyanotic episodes can be treated with phenylephrine. -Maintain adequate blood volume and venous return. -Avoid myocardial depressants, because any decrease in right ventricular contractility can decrease pulmonary circulation. -If pulmonary vascular disease is present, invasive pulmonary artery catheter monitoring as well as vasoactive agents may be necessary.
L to R Shunt (e.g.VSD, ASD)	(+)The decrease in SVR decreases the left-to-right shunting. (-)The increase in blood volume can precipitate failure because the patient is in a state of compensatory hypervolemia.	-Avoid excessive fluid administration, over-transfusion, and Trendelenburg position. -Avoid increases in SVR.

SVR= systemic vascular resistance, LV= left ventricular, , TOF= tetralogy of Fallot, CCHD= cyanotic congenital heart disease, VSD= ventricular septal defect, ASD= atrial septal defect.

Anesthesia for Cesarean Delivery

The anesthesiologist must provide general or regional anesthesia for surgical anesthesia for cesarean delivery. Regional anesthesia is typically preferred unless the patient is anticoagulated (risking spinal hematoma) or is critically ill and thereby unable to lie flat or maintain their airway. Further, with some CHDs, such as Fontan circulation, maintenance of spontaneous respirations with a neuraxial approach may result in more optimal hemodynamics. Alternatively, general anesthesia may be dictated by obstetric or anesthetic indications.

If regional anesthesia is chosen, then the anesthesiologist must decide between a single-shot spinal, an epidural, a combined spinal-epidural (CSE), or a continuous spinal technique. The rapid decrease in preload and afterload associated with a single shot spinal may carry additional risk in some cardiac lesions (eg, severe mitral stenosis, severe aortic stenosis, aortic coarctation, or patients at risk for right-to-left shunting). An arterial line placed prior to the spinal anesthetic with a carefully titrated phenylephrine infusion initiated at the time of the spinal anesthetic may provide adequate hemodynamic stability. On the other hand, an epidural dosed slowly with appropriate vigilance is likely to result in the least cardiovascular disruption. Addition of an opioid when dosing the neuraxial anesthetic will reduce the amount of local anesthetic required while improving both intraoperative and postoperative analgesia. The elimination of epinephrine from the epidural test dose or loading dose will eliminate the possible deleterious effects of systemic epinephrine.

An epidural, however, may not provide the density of block that intrathecal local anesthetics provide. An excellent alternative to a single-shot spinal or epidural technique is a low-dose CSE technique which has been reported successful in high-risk cardiac patients.[13] A low-dose CSE technique is performed with an intrathecal dose of 4 to 5 mg of heavy bupivacaine along with 15 to 20 mcg fentanyl and long-acting opioid. This is followed by slow loading of the epidural local anesthetic (eg. 2% lidocaine) to achieve a T4 surgical level. The benefits of the low-dose CSE technique include slow-onset of the neuraxial block, which allows the anesthesiologist to maintain preload and afterload during the onset, while still achieving the greater block reliability of intrathecal local anesthetic administration.

The anesthesiologist must remain vigilant during the onset of neuraxial surgical or analgesic anesthesia. Maintaining uterine blood flow is important for fetal well-being and, in patients with intravascular shunting, maintaining systemic vascular resistance is important for preventing worsening cyanosis. Cautious intravenous hydration and/or gentle titration of a phenylephrine infusion or ephedrine boluses are options to counteract the hemodynamic effects of surgical neuraxial block.

Management of Hemorrhage

It is important for the anesthesiologist to know the hemodynamic effects of various uterotonic agents and avoid those that would be deleterious in particular lesions.

Table 5. **Uterotonic Use in Patients with Cardiac Disease**

Drug	Cardiopulmonary effects	Lesions to avoid Agent or Use with Caution	Notes
Oxytocin	↓ MAP Slight ↑ PAP	Aortic stenosis HOCM Ischemic disease Aortopathy with risk of dissection	-Most effective uterotonic agent -Administer cautiously and slowly (via pump) in patients intolerant of ↓ MAP -Consider counteracting ↓ MAP with phenylephrine infusion -Do not administer in bolus IV form in patients with cardiac disease
Methergine	Can cause sudden profound: ↑ SVR ↑ PVR	Hypertension, Preeclampsia Pulmonary HTN Ischemic disease Intracardiac shunts	-Generally avoided in cardiac patients
Carboprost (Prostaglandin F2 alpha)	↑↑↑PAP Bronchospasm → ventilation perfusion mismatch	Fontan circulation Intracardiac shunt Pulmonary HTN	-Do not use in patients who cannot tolerate increased PA pressure.
Misoprostol	None	None	-The least effective uterotonic agent. -Can be used prophylactically

MAP = mean arterial pressure, PAP = pulmonary artery pressure, SVR = systemic vascular resistance, PVR = pulmonary vascular resistance, PAP = pulmonary arterial pressure, HTN = hypertension

Beta Agonist Drugs in Labor

Beta agonist drugs such as terbutaline are occasionally used in labor to urgently relax the uterus when uterine hyperstimulation or tachysystole results in fetal compromise. It is important for the obstetric team to be aware that this drug is contraindicated in some cardiac lesions. Patients with Hypertrophic Obstructive Cardiomyopathy (HOCM) could have infundibular spasm and/or worsen their outflow gradient as a result of beta agonism. Likewise, patients who would not tolerate tachycardia or patients with a history of tachyarrhythmias should not receive beta agonist drugs in labor.

Arrhythmias and Management of Cardioverter Defibrillators during Labor

Patients with a history of tachyarrhythmias are at risk of experiencing their arrhythmia during labor which can result in fetal compromise.[14] Patients with a history of arrhythmias should have 5-lead ECG monitoring during labor. Maternal cardioversion can be performed in pregnancy. If the patient has a fetal scalp electrode, this should be removed prior to the cardioversion. Automatic implantable cardioverters defibrillators should be left "on" in labor as these provide the most rapid response to a tachyarrythmia. A magnet should be immediately available to use in the event of an emergent cesarean delivery requiring unipolar cautery.

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ANESTHESIOLOGY 2017
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Difficult Airway Management in Pediatrics: Approaches for Success

Narasimhan Jagannathan, MD **Chicago, IL, USA**

GENERAL CONSIDERATIONS

Management of the pediatric airway poses its own unique challenges compared to the adult airway. Anatomically, small children (infants) have a more cephalad larynx, floppier epiglottis, larger tongues, smaller mouth opening, and are more prone to rapid oxygen desaturation due to their higher rates of oxygen consumption.

The management of the pediatric airway has experienced a number of changes in the past decade. Equipment advancements in pediatric sizes and pediatric-specific algorithms have improved the options available to the clinician.

Current and ongoing clinical trials have helped define the role of these newer devices and their effectiveness in the pediatric population.

Fundamentally, oxygenation is the most critical function of airway management. Methods to ensure gas exchange should be governed by the patient's medical condition, the clinical scenario, and the resources available. *A recent multicenter study of over a thousand children with difficult airways found that the most common severe complication was cardiac arrest, occurring in 2% of these children from persistent hypoxemia. The most common complication overall was hypoxemia (SPO2 < 85%).*

The child with a difficult airway may manifest as the inability to mask ventilate, perform direct laryngoscopy, or both. Multiple factors, including disease processes involving the airway, can impair access to the airway and ventilation.

Independent risk factors associated with complications during management of the pediatric difficult airway:

a. Short thyromental distance (micrognathia)
b. Weight less than 10 kg
c. Greater than two tracheal intubation attempts
d. Three direct laryngoscopy attempts before an indirect technique (e.g. videolaryngoscopy, fiberoptic bronchoscopy)

INCIDENCE OF DIFFICULT AIRWAY

The unanticipated difficult airway occurs less frequently in children than in adults

The overall incidence of the difficult airway in children is less than in adults, is especially rare in healthy children. Some studies have found that the incidence of difficult mask ventilation in children was 0.2% (vs. 1.4% in adults); and incidence of difficult laryngoscopy was 0.06%-4.7% (vs. 1.5%-8.5% in adults). *Most notably, children less than 1 year of age are more likely to have an increased incidence of difficult laryngoscopy (4.7%; Cormack & Lehane Grade III or higher)*. There exists an 80% rate of anticipated difficult airways in children. There appears to be a 20% unanticipated difficult airway rate, which is greater than what has been traditionally taught to anesthesia practitioners.

THE ANTICIPATED DIFFICULT AIRWAY

Pediatric difficult airways are often anticipated, as they are typically associated with dysmorphic features, which are usually recognized during the preoperative assessment.

Craniofacial syndromes are the most common reason for difficult airways in the pediatric population

Micrognathia is the most common physical finding associated with difficult laryngoscopy in an infant

A meticulous history and physical examination can reveal important findings that are predictive of a difficult airway and may help localize the site of airway obstruction.

Detecting potential abnormalities pre-operatively will allow the clinician to formulate an adequate plan for airway management prior to the induction of anesthesia.

A practical approach is to classify the child according to the functional abnormality and associated condition (Table 1). It is also critical to determine if there is enough of a mouth opening to allow for the insertion of the airway device one plans to use (i.e. Supraglottic airway (SGA) or videolaryngoscope).

Depending on the age of the child and the type of syndrome, anatomic changes related to the growth of the child can either improve or worsen as the patient ages (Table 1)

THE UNANTICIPATED DIFFICULT AIRWAY

The unanticipated difficult airway, is likely to occur after induction of general anesthesia, and should prompt early recruitment of additional resources (call for help, ENT surgeon)

Iatrogenic injures of the airway can occur from multiple intubation attempts that can lead to bleeding and supraglottic edema, even with gentle instrumentation.

No single method has been proven to be effective in all patients; the airway management plan in these situations should be tailored to the specific patient's condition and the availability resources.

Limiting the number of direct laryngoscopy attempts to avoid airway trauma, and use of alternative devices, including videolaryngoscopy, use of supraglottic airways (SGAs) for rescue, and/or as a conduit for fiberoptic guided tracheal intubation are potential options.

MANAGEMENT STRATEGIES

A true 'awake' intubation is often impractical in children and seldom utilized. Exceptions may be considered when difficult mask ventilation is predicted, there is severe upper airway obstruction at rest (i.e. mucopolysaccaradosis and Treacher Collins syndrome), or 'full stomach' precautions are needed. The following scenarios may warrant consideration of an awake intubation in a child: a patient that is predicted to be a potential difficult laryngoscopy AND has any of the following: 1) high aspiration risk; 2) severe upper airway obstruction at rest; 3) predicted difficult mask ventilation. The awake patient has the ability to maintain their own oxygenation and ventilation, avoid worsening airway obstruction, and can better protect their airway from aspiration of gastric contents.

In clinical practice, the majority of anticipated difficult airways are managed after induction of general anesthesia, while maintaining spontaneous ventilation. Pharmacologic agents such as sevoflurane, ketamine, dexmedetomidine, and topicalization of the airway with local anesthetics may provide adequate conditions for airway manipulation while minimizing reflex activation of the airway and respiratory depression.

The use of NMBDs in the management of children with difficult airways vs. maintenance of spontaneous ventilation remains a controversial topic. The use of NMBDs after sevoflurane inhalational induction has been associated with fewer adverse respiratory events in children with normal airway anatomy when compared with sevoflurane without NMBDs. In contrast, there is little evidence on the effects of NMBDs in children with abnormal airway anatomy.

Consideration should be given to whether native muscle tone is needed to maintain airway patency when making the decision to use NMBDs (i.e. anterior mediastinal mass). In such cases, avoidance of NMBDs may be warranted.

*The use of an awake SGA or modified nasal trumpet (*a nasopharyngeal airway is inserted into the patient, and then fitted with an endotracheal tube adapter that is connected to an oxygen source) *will allow the clinician to provide oxygen, continuous positive airway pressure, bypass airway obstruction, and allows the option of delivering inhaled agents (sevoflurane), if a spontaneous breathing technique under anesthesia is needed*.

Figure 1 is proposed algorithm for the management of the unanticipated difficult airway in children. (Adapted From the 2013 ASA Guidelines)

DEVICES USED IN THE MANAGEMENT OF DIFFICULT AIRWAYS

Various intubation techniques and devices are currently available in the pediatric anesthesia population, but their clinical usefulness are not well assessed, particularly in children with difficult airways.

A clinical registry collecting information of 1603 pediatric anesthesia cases with difficult tracheal intubation with conventional direct laryngoscopy revealed similar first attempt success rates for fiberoptic intubation via supraglottic airway and videolaryngoscopy. However, in infants, fiberoptic intubation via a supraglottic airway was more successful than the use of videolaryngoscopy.

Flexible Fiberoptic bronchoscope

The flexible fiberoptic bronchoscope remains the "gold standard" for securing the airway in the face of a difficult tracheal intubation, despite the availability of newer videolaryngoscopes.

The major advantage is its versatility of use, allowing for intubation of the trachea via the oral route, nasal route, or through an SGA. It can also be used to evaluate the lower airways as well as assist in the positioning of bronchial blockers and double lumen tubes. Table 2 summarizes the advantages and limitations with various routes used for fiberoptic intubation,

The fiberoptic bronchoscope is available in sizes appropriate even for neonates. The smallest fiberoptic scope is 2.2 mm in diameter (ultra-thin). A limitation of the ultra-thin bronchoscope is the lack of a suction channel. A disadvantage of fibreoptic bronchoscopes is the vulnerability of the image quality to secretions and blood in the airway. Maneuvering of the bronchoscope can be challenging (especially with the ultra-thin bronchoscopes). The learning curve is steep and requires practice and regular use to acquire and maintain one's skill.

Videolaryngoscopes

The use of video or optical laryngoscopes has gained popularity as an alternative to flexible fiberoptic bronchoscopy guided tracheal intubation. These devices combine a fiberoptic bundle or video camera on an intubating blade that may be fixed or malleable, and displays the laryngeal view on a screen or eyepiece. The ASA difficult airway algorithm strongly suggests using a videolaryngoscope as the initial approach in a patient with suspected difficult airway.

These devices require less head and neck mobilization compared with direct laryngoscopy (DL), and may be useful in patients with cervical instability.

Some studies suggest videolaryngoscopes can improve the glottic view when compared with traditional DL, but at the expense of increased time for tracheal intubation. However, the greater time to intubation may be acceptable, if the improved laryngeal grade of view allows for successful tracheal intubation, particularly in situations where DL has failed. Common advantages and disadvantages of videolaryngoscopes vs direct laryngoscopes are presented in Table 3.

Pediatric sizes are available for the GlideScope Video Laryngoscope (Verathon, Bothell, Washington, USA), Airtrach Disposable Optical Laryngoscope (Prodol Meditec, Vizcaya, Spain), Pentax AWSTM (Pentax Corporation, Tokyo, Japan), Stortz DCITM Video Laryngoscope (Karl Storz, Tuttlingen, Germany), Truview PCD Infant (Truphatek, Netanya, Israel), McGrath airway scope (Teleflex, Triangle Park, NC.), and Bonfils optical stylet (Karl Storz, Tuttlingen, Germany)

Supraglottic airway devices (SGA):

The effectiveness of SGAs has helped establish their role in the management of children with difficult airways. An SGA may be able to bypass obstructions at the supraglottic level, and be a useful rescue device by improving airway patency. This is particularly true in children with airway obstruction at birth (e.g. Pierre Robin Syndrome) where SGAs can be placed in the awake state.

These devices may also be helpful in patients that may otherwise be difficult to mask ventilate, and can be used as a temporary or primary means to maintain ventilation if difficult or failed intubation is encountered. Additionally, they can also be used as a conduit for fiberoptic tracheal intubation. It is important to use specifically designed SGAs as a conduit for fiberoptic guided tracheal intubation (e.g. air-Q, Ambu Aura), as these devices a shorter and wider bored to accommodate cuffed tracheal tubes.

It is important to note that with the placement of an SGA, the anatomic position does not necessarily correlate to the functional quality of the airway: varying degrees of epiglottic downfolding may be present, even with adequate ventilation through the SGA. Epiglottic downfolding is a common finding in SGAs, especially in small children

(<10kg). Therefore, visualization techniques (e.g. fiberoptic assisted) may have increased success compared with blind techniques when tracheal intubation is attempted.

There are several different SGAs on the market; each of them has advantages and disadvantages as determined by their specific features Table 4 presents the SGAs that have been studied and used in children.

CANNOT INTUBATE, CANNOT OXYGENATE:

The “cannot oxygenate, cannot intubate” (CICO) scenario is a rare event in children, and represents a very challenging and resource limited situation.

The best way to approach this situation in small children is still unclear. A specific anatomic feature in the pediatric airway, such as the proportionally smaller cricothyroid membrane, especially in infants and neonates, significantly reduces the success of trantracheal catheter placement.

Data suggests that success rates of needle cricothyrotomy can be as low as 65.8%, and information is lacking regarding the adequacy of ventilation using these methods in small children.

Needle/cannula cricothyrotomy has been proposed as the most expeditious approach for invasive tracheal access, when ENT surgical intervention is not immediately available. Even in skilled hands, a high rate of complication, including posterior tracheal wall puncture can occur.

When a cricothyrotomy is necessary, a device designed specifically for this purpose should be used, such as a Ravussin jet ventilation catheter (Cook Medical; Bloomington, IN USA).

A makeshift device consisting of an angiocatheter (at least 18 G), a 3 ml syringe, and 3.0 mm ID tracheal tube adapter may be an alternative if commercial kits are not available. If possible, a kink-resistant angiocatheter may be preferable when using this technique.

An Enk Oxygen Flow Modulator™ (Cook Medical, Bloomington, IN, USA) may be used for oxygenation, at 1 L per year of age flow rate, and providing enough time to allow expiration.

The use of jet ventilation through transtracheal catheters is associated with an increased rate of complications and barotrauma, even in a controlled setting. Adequate oxygenation has shown to be possible through transtracheal catheters without the use of jet ventilation in animal and bench studies.

It is important to remember that needle cricothyrotomy only provides a temporary means for oxygen insufflation and that effective ventilation may not be possible.

Future studies on scalpel techniques are needed to determine if this may be a more effective option in the CICO situation.

FIGURE 1. PROPOSED ALGORITHM FOR THE MANAGEMENT OF THE UNANTICIPATED DIFFICULT AIRWAY IN CHILDREN. (Adapted from the 2013 ASA Guidelines)

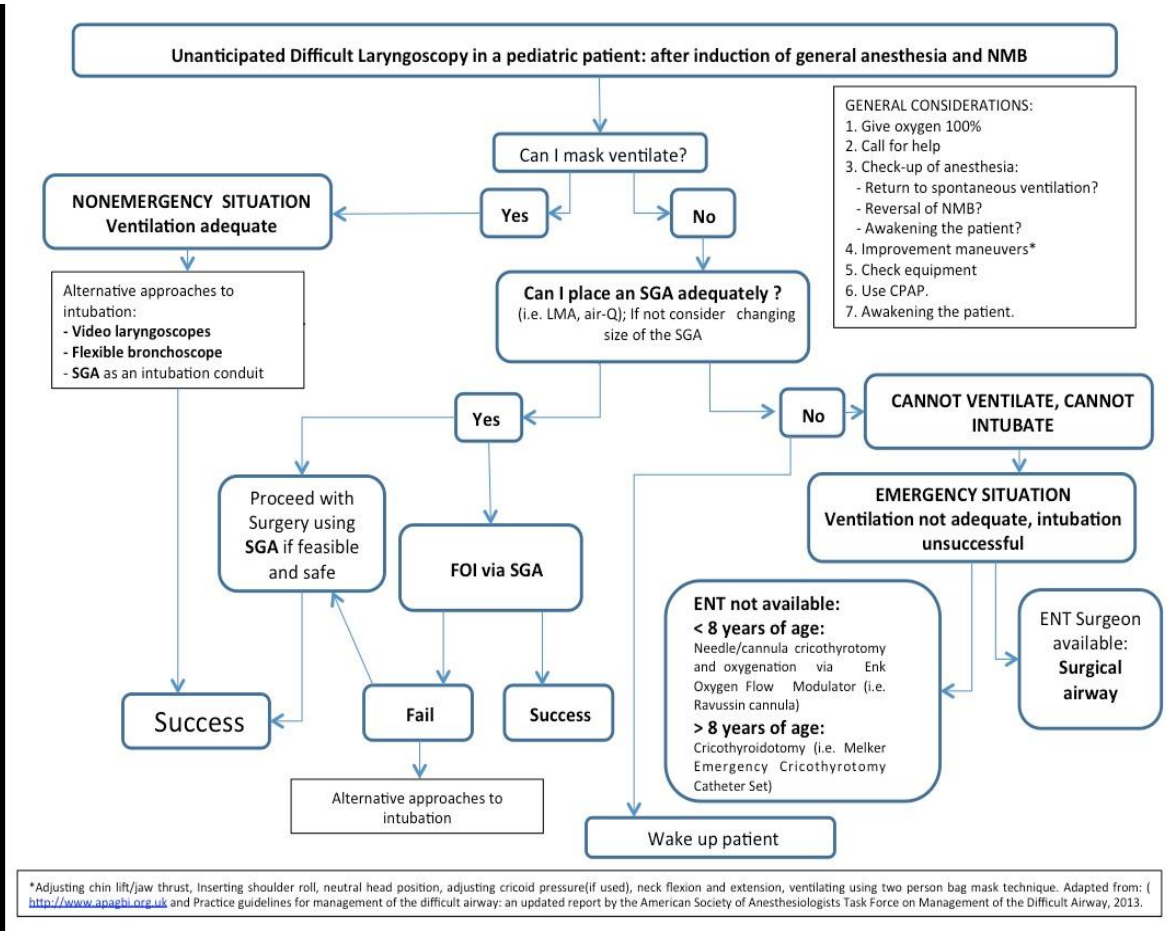

TABLE 1. FUNCTIONAL CLASSIFICATION OF CONDITIONS ASSOCIATED WITH DIFFICULT AIRWAY

Functional Classification	
Supraglottic Abnormalities	**Maxillary hypoplasia:** Apert syndrome Crouzon syndrome Pfeiffer syndrome Saethre-Chotzen syndrome DiGeorge syndrome **Mandibular hypoplasia:** Pierre Robin sequence Treacher Collins Goldenhar syndrome Sticklers syndrome Mobius syndrome Micrognathia CHARGE association
Abnormalities of the whole airway including the glottis	**Mucopolysaccharidoses:** Hurler syndrome Hunter syndrome Sanfilipo syndrome Morquio síndrome Maroteaux-Lamy syndrome **Vascular lymphatic malformations:** Beckwith-Wiedemann syndrome
Chronic Subglottic Abnormalities	Subglottic stenosis Laryngeal stenosis Tracheal stenosis Laryngo/tracheomalacia Masses (neck/parapharyngeal)
Poor mouth opening or mobility of jaw, neck	Freeman-Sheldon Noonan syndrome Spinal fusion Cervical stenosis Cervical Instability
Other abnormalities	Infections Burns Miscellaneous Sturge-Weber syndrome Robinow syndrome

TABLE 2. A COMPARISON BETWEEN DIFFERENT FIBEROPTIC INTUBATION (FOI) APPROACHES

	Advantages	Limitations
Oral	• Shorter path to the larynx vs. nasal route • Avoids shearing of adenoidal tissue and epistaxis	• Patient can bite bronchoscope • Greater skill required to maneuver the scope
Nasal	• Simpler midline placement • Relatively straightforward path to larynx • Easier to acquire skills • Useful in children with extremely limited mouth opening • Avoids the risk of the child biting the scope	• Potential risk for epistaxis and/or adenoidal tissue shearing • Sinusitis
Supraglottic airway assisted	• Provides a hands free airway • Relatively straightforward path to the larynx • Ability to overcome upper airway obstruction • Can oxygenate and provide inhaled anesthetic during intubation • Specific SGAs designed for intubation are available (ie. air-Q, Ambu Aura-i)	• Modifications of equipment needed for some SGAs (ie. LMA Classic), especially when using a cuffed TT

TABLE 3 ADVANTAGES AND LIMITATIONS OF VIDEOLARYNGOSCOPY AND DIRECT LARYNGOSCOPY IN CHILDREN

	Videolaryngoscopy	Direct laryngoscopy
Advantages	-Improved glottic views in known difficult airways -Less force needed to displace soft tissue to obtain an adequate glottic view -Provides a more anterior view of the glottis -Port for oxygen delivery (in certain models) -Allows glottic view to be displayed onto an external monitor -Less levering of the maxillary teeth -No need to sweep & displace the tongue	-Long history of efficacy in management of the pediatric airway -Faster times for tracheal intubation in the normal airway -Several sizes of blades available
Disadvantages	-Longer times for tracheal intubation in the normal airway -Increased hand-eye coordination required -Impractical for patients with small mouth opening -More expensive -Soiled airway (blood, vomit) will obscure the lenses -Complications: perforation of the palatopharyngeal arch and soft palate have been reported	-Poorer glottic views in known difficult airways→ poor technique in the difficult airway -Requires direct line of site to glottis for an adequate view -Greater work force required -Large tongues may be difficult to displace -Impractical for patients with small mouth opening

		-Complications: airway edema; greater complications such as hypoxemia, dental trauma

TABLE 4. SUPRAGLOTTIC AIRWAY DEVICES AVAILABLE FOR CHILDREN

Device	Advantages	Disadvantages
Classic LMA/ LMA Unique™ (Teleflex, Triangle Park, NC)	• Long history of safety and efficacy • Large evidence base	• In infants: delayed airway obstruction (<10kg) • Have to modify when using it for fiberoptic intubation • No gastric drain provision
ProSeal LMA™ (Teleflex, Triangle Park, NC)	• Long history of safety and efficacy • Large evidence base • Gastric drain tube • Higher leak pressure than LMA classic • Stable In small children	• No single-use version • Narrower lumen of airway tube makes tracheal intubation through this device more challenging
air-Q™ (Mercury Medical Clearwater, FL)	• Designed for tracheal intubation • Large evidence base for difficult airway management • Can accommodate cuffed tracheal tubes • Stable In small children	• No gastric drain provision
Supreme LMA™ (Teleflex, Triangle Park, NC)	• Single-use • Gastric drain tube • Higher leak pressure than LMA classic	• Not suitable for fiberoptic-guided intubation secondary to narrow airway tube
i-Gel™ (Intersurgical, Wockingham, UK)	• Higher leak pressures • Gastric drain tube • Favorable fiberoptic views	• Tendency to spontaneously dislodge after placement in small children • Laryngeal bulging observed in small children • Small sizes (1, 1.5) cannot accommodate cuffed tracheal tubes

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Outpatient Total Knee Arthroplasty: How Do We Get There?

Girish P. Joshi, MBBS, MD, FFARCSI **Dallas/Texas**

With aging of the population worldwide, it is projected that the demand for total knee arthroplasty (TKA) will increase significantly [1], which will increase healthcare costs [2]. The introduction of alternate payment systems such as bundled payments [2], has led to the emphasis on reducing hospital length of stay (LOS) through implementation of evidence-based enhanced recovery clinical pathways (Table 1), particularly approaches to postoperative pain control [3-6]. In addition, advances in surgical techniques including smaller muscle sparing incisions (due to availability of smaller instrumentation and prosthesis) and avoidance of patellar eversion and knee dislocation and hyperflexion minimizes tissue trauma and reduces postoperative inflammation and pain [7] allow TKA to be performed on a short-stay or outpatient basis [8,9]. This refresher course addresses the current evidence and controversies regarding the perioperative care of patients undergoing outpatient TKA.

Preoperative Considerations

Patient Selection

It is well recognized that patient selection can influence perioperative complications and postoperative unplanned admission and readmission rates [10,11]. However, the current literature on optimal patient selection for ambulatory TKA is sparse. Appropriate patient selection should consider the complex interplay between the surgical procedure, patient characteristics, anesthetic technique (e.g., spinal anesthesia [SA] *versus* general anesthesia [GA]), and social factors. The exclusion criteria commonly used for TKA include age >80 years, body mass index (BMI) >40 kg/m^2, ASA physical status >3, use of anticoagulation therapy, physical disability (e.g., use of walking aids) or frailty, malnutrition, psychiatric disorders (psychopharmacologic therapy) [12,13], and inadequate social structure.

Preoperative Evaluation and Optimization of Comorbidities

Preoperative evaluation and optimization of comorbid conditions is critical to improving perioperative outcomes. The key modifiable risk factors associated with complications that should be considered preoperatively include glycemic control [14,15], smoking status [16], nutritional status, and anemia [17-19]. Appropriate optimization should reduce the risks of surgical site infection and pulmonary complications among others. In addition, anemia is associated with increased dizziness and orthostatic hypotension, which may delay ambulation and discharge home. Identifying patients with preoperative anemia and treating with erythropoietin and/or iron supplements has been shown to reduce the need for perioperative blood transfusion and postoperative complications.

Preoperative Patient Education

Preoperative education is essential to achieve realistic expectations [20], which should help alleviate the psychological stress and anxiety associated with TKA [21]. Patient education should include the entire perioperative experience and make the patient an active participant, which should ensure that optimal care is continued upon discharge [22].

Prehabilitation

Prehabilitation includes cardiopulmonary conditioning and muscle strengthening [23,24], has been shown to improve postoperative rehabilitation by reducing frailty and disability. However, the specific of an optimal program are lacking. One approach is to have the patient perform the postoperative rehabilitation exercises several weeks prior to surgery. This should facilitate rehabilitation and may allow early return to daily living activities.

Intraoperative Considerations

Choice of Anesthetic Technique

The anesthetic options available for TKA include SA or GA. The use of SA avoids the potential adverse effects associated with the drugs used to provide GA, including cardiopulmonary depression and residual muscle paralysis.

Several studies have reported reduced postoperative complication rate as well as hospital LOS with the use of SA, as compared with GA [25,26]. Therefore, SA is generally preferred for patients undergoing TKA. It is critical that when considering SA in the outpatient setting, intrathecal opioids (e.g., fentanyl or morphine) must be avoided due to their adverse effects (e.g., urinary retention, respiratory depression, and pruritus). One of the limitations of SA, in the ambulatory setting, is that it may delay ambulation due to muscle weakness and postural hypotension, and thus may delay discharge home. Therefore, in the ambulatory setting, a fast track general anesthetic technique is generally preferred [27].

An ideal fast-track GA technique should provide rapid recovery with minimal or no residual adverse effects from hypnotic-sedatives, opioids and muscle relaxants. Therefore, it is necessary to avoid premedication with midazolam [28,29] and avoid deep anesthesia, as it may delay emergence from anesthesia. Maintenance of anesthesia with inhaled anesthetic and 50% nitrous oxide (N_2O). The amnestic and analgesic properties of N_2O reduce inhaled anesthetic and opioid requirements and facilitate recovery [30-32]. However, N_2O is usually avoided because of concerns of increased postoperative nausea and vomiting (PONV), although recent data shows that the incidence of PONV with or without N_2O is similar. Thus, there is no convincing reason to avoid N_2O. Because even minimal postoperative residual paralysis (train-of-ratio ratio <0.9) can increase the incidence of critical respiratory events in the recovery room, increase the need for reintubation, and prolong recovery time, muscle relaxants should be used sparingly and any residual paralysis reversed with adequate doses of reversal agents [33].

Most importantly, because intraoperative opioid overdose can only be recognized at emergence of anesthesia when the patient's spontaneous ventilation is delayed, it is imperative that opioids are administered judiciously. Reducing the doses of intraoperative opioids should reduce the risk of developing opioid-induced hyperalgesia and avoid increased postoperative pain and opioid requirements [34]. Intraoperative administration of opioids is usually guided by hemodynamics (i.e., increased heart rate and/or blood pressure); however, attempts to achieve a "tight" control may result in increased opioid administration. Also, opioids should not be administered to correct tourniquet-induced hypertension and tachycardia. It is common practice to administer a long-acting opioid towards the end of surgery, as a plan for postoperative analgesia. Assuming that the intraoperative dose of opioid is minimal, a predetermined morphine (~0.1 mg/kg, IBW) or hydromorphone (~10 mcg/kg. IBW) may be administered 20-30 min prior to expected time of tracheal extubation to achieve adequate pain relief at emergence without delaying tracheal extubation [35,36]. The use of non-opioid analgesics to reduce the opioid-related adverse effects should minimize postoperative complications and expedite recovery [6].

Antiemetic Prophylaxis

PONV is one of the common factors that can delay recovery. Therefore, aggressive PONV prophylaxis is recommended to improve postoperative outcomes and facilitate early mobilization. Although risk-based approaches for antiemetic therapy have been proposed, the compliance with these strategies has been shown to be poor. Therefore, routine prophylactic multimodal antiemetic therapy should be utilized [37]. The number of antiemetic combinations could be based on the patient's level of risk. A combination of dexamethasone 8 mg, IV (after induction of anesthesia) and ondansetron 4 mg, IV (at the end of surgical procedure) could be used for most patients. Patients at very high risk of PONV (e.g., history of motion sickness, history of previous PONV, high opioid requirements for pain relief) may receive additional antiemetic therapy such as preoperative transdermal scopolamine and/or total intravenous anesthesia. Patients requiring rescue antiemetic therapy in the immediate postoperative period could receive low-dose promethazine (6.25 mg, IV) or dimenhydrinate (1 mg/kg). Post-discharge nausea and vomiting (PDNV) is a common and sometimes severe adverse outcome for ambulatory patients [38]. One of the major predictor of PDNV is postoperative opioid use. Therefore, opioid dose after discharge home should be limited.

Analgesic Techniques

Postoperative pain is one of the most common reasons for delayed recovery and unplanned admission and readmission after TKA. Also, inadequate pain control in the immediate postoperative period is one of predictors of persistent postoperative pain, which occurs in about 44% of TKA patients [39,40]. Therefore, aggressive postoperative pain management is critical. Planning for perioperative pain management should be initiated preoperatively. Patients scheduled for TKA typically have chronic pain and therefore may receiving analgesics (e.g.,

non-steroidal anti-inflammatory drugs [NSAIDs]), which are commonly discontinued prior to surgery. However, this can increase preoperative pain, which is associated with increased postoperative pain [7]. Therefore, preoperatively discontinued analgesic should be replaced with appropriate alternative analgesics.

Multimodal analgesia technique (Table 2), which includes combination of non-opioid analgesics improve pain relief and reduce opioid requirements [6]. This should reduce opioid related side effects (e.g., sedation, nausea, vomiting, urinary retention, ileus, urinary) that can delay recovery and limit the recent concerns of abuse [41]. Commonly used non-opioids include acetaminophen and NSAIDs or cyclooxygenase (COX)-2 selective inhibitors, which form the basis of a multimodal analgesic technique [42-44]. In addition, a single intraoperative dose of dexamethasone should be administered, as it an analgesic as well as an antiemetic and does not increase complications [45-49]. Also, gabapentinoids [gabapentin and pregabalin]) have been used as analgesic adjuncts; however, recent systematic reviews and meta-analyses have questioned their benefits [50,51]. Although ketamine has been used as an analgesic adjunct, there is lack of consistent benefits [52,53]. Therefore, its routine use in patients undergoing TKA is questioned [6].

These analgesics and adjuncts should be supplemented with a peripheral nerve block and/or periarticula infiltration [54]. In recent years, adductor canal block has replaced femoral nerve block, because femoral nerve block can cause quadriceps weakness and delay ambulation [55-58]. Concerns with peripheral nerve blocks have led to the use of periarticular infiltration analgesia that has been shown to provide excellent pain relief, reduce opioid requirements, and facilitate ambulation [59]. Therefore, periarticular infiltration is rapidly becoming the standard of care. Periarticular infiltration involves a meticulous infiltration of all layers of the surgical incision under direct vision immediately prior to tissue/skin closure. Although there is some suggestion that periarticular infiltration and adductor canal block should be combined, the benefits of combination remain controversial.

Other Factors

The use of the antifibrinolytic, tranexamic acid (TXA) has been gaining prominence as a method to minimize perioperative blood loss and need for blood transfusions. TXA is a lysine analog that inhibits plasminogen activation, thereby preventing the cleaving of fibrin and clot breakdown. While theoretically TXA may increase the risk of a blood clot, recent meta-analyses have proven its efficacy and safety [60-62]. Although there is some variability in dosing, a common regimen includes administering 1 gm, IV before incision followed by 1 gm at the end of surgery. The contraindications for TXA are included in table 3.

Postoperative Considerations

The primary aim in the immediate postoperative period is early mobilization and the initiation of physical therapy as soon as possible. The factors that delay ambulation include pain, PONV, and orthostatic intolerance. Prior to discharge home, patients should be assessed for their ability to independently move from the supine position to a standing position and vice versa. Next, they should be assessed for the ability to independently transfer from a chair to a standing position and ambulate at least 100 feet without assistance.

Post-discharge Considerations

Factors that influence recovery and the ability to engage in physical therapy at home include, PONV, fatigue, pain, sleep disturbances, and social constraints [63,64]. Quadriceps muscle strength is reduced by 85% after a TKA [65,66], which highlights the necessity of physical therapy after discharge for preservation of muscle mass and function. Typically, home physical therapy is performed three times a week for a period of 2-3 weeks. Readmission after TKA is usually due to surgical (55%) causes (e.g., infection, hematoma, pulmonary embolus, deep vein thrombosis) and medical (45%) causes [67]. An analysis of the NSQIP database (2011-2013) compared outcome after TKA and THA performed as fast-track inpatient (LOS≤2 days) and outpatient (LOS<1 day) found that outpatients experience higher rates of post-discharge complications (6.7% within the outpatient cohort and 1,4% in the fast-track cohort). The major complication was postoperative bleeding and need for blood transfusion. There were no differences in the readmission rates (2.4% outpatient vs. 2.0% inpatient) [68]. Unfortunately, the authors did not provide separate data for inpatient and outpatient populations. Also, the data included in the study are older and thus may not reflect current perioperative care principles.

Summary

Ambulatory TKA is feasible, safe, and cost-efficient. It is necessary to develop comprehensive, multidisciplinary, clinical pathways that involve the entire perioperative team (e.g., surgeons, anesthesiologists, nurses, physical therapists, occupational therapists, and ancillary staff). The clinical pathways are continuing to evolve as the experience with ambulatory TKA accumulates and new information is obtained. Further research is needed in the area of postoperative management in regards to optimal type, timing, and duration of physical therapy, as well as factors that influence readmission.

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Table 1: Overview of Enhanced Recovery Protocol for Ambulatory Total Knee Arthroplasty

Preoperative Care

- Preoperative assessment, screening, and optimization of comorbid conditions
- Prehabilitation
  - Muscle strengthening and cardiovascular conditioning
  - Nutritional support
  - Avoidance of dehydration
- Patient and family education
- Discharge planning

Intraoperative Care

- Minimally invasive surgical approach
- Spinal vs. General anesthesia
- Optimal opioid-sparing multimodal pain management
- Multimodal antiemetic prophylaxis
- Tranexamic acid

Postoperative Care

- Opioid-sparing multimodal analgesia
- Early physical therapy
- Early mobilization
- Promotion of independence and participation

Table 2: Opioid-sparing Multimodal Analgesia Options for Ambulatory TJA

Preoperative Analgesia

- Acetaminophen
- Cyclo-oxygenase-2 inhibitors (e.g., celecoxib)
- Gabapentin/pregabalin

Intraoperative Analgesia

- Abductor canal block
- Periarticular infiltration
- Dexamethasone

Postoperative Analgesia

- Acetaminophen
- Non-steroidal anti-inflammatory drug or cyclo-oxygenase-2 inhibitors
- Gabapentinoids (gabapentin and pregabalin)
- Opioids as rescue

Table 3: Potential Contraindications For Tranexamic Acid (TXA)

- Allergy to TXA or any component of the formulation
- Active intravascular clotting
- Subarachnoid hemorrhage
- Active thromboembolic disease (e.g., cerebral thrombosis, deep vein thrombosis, pulmonary embolism)
- History of thrombosis or thromboembolism, including retinal vein or retinal artery occlusion
- Intrinsic risk of thromboembolism (e.g., hypercoagulopathy, thrombogenic cardiac rhythm disease, thrombogenic valvular disease)
- Concurrent use of combination hormonal contraception
- Cardiac stent placement within a year
- Acquired defective color vision

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What's New in Teaching and Learning Regional Anesthesia?

Edward R. Mariano, MD, MAS **Palo Alto, CA**

The use of ultrasound guidance in the practice of regional anesthesia arguably began in the late 1980s (1), although ultrasound Doppler technology was used to direct needle insertion for peripheral nerve blockade in the 1970s (2). This past decade has seen a rapid increase in practical applications and clinical research in the field of ultrasound-guided regional anesthesia (UGRA), and the American Society of Regional Anesthesia and Pain Medicine (ASRA) and European Society of Regional Anesthesia have even published joint committee guidelines for training in this discipline (3). Given the rapid evolution of UGRA, evidence to support this practice was initially limited; however, years later many studies have now firmly established the important role of ultrasound guidance in regional anesthesia (4,5).

The Learning Curve for Regional Anesthesia

Many of our pre-conceived notions regarding the learning curve for regional anesthesia procedures come from a study conducted over 20 years ago involving epidural and spinal blocks (6). The results of this study demonstrate that 90% success rates could not be achieved until 45 spinal and 60 epidural procedures had been performed (6). The performance of neuraxial and peripheral nerve block procedures are clearly different; yet these "magic numbers" of 45 and 60 seem to have been applied quite broadly in anesthesiology training. Since regional anesthesia practice has evolved to include ultrasound for nerve localization, the learning curve has been reevaluated.(7) In an early study of novices during performance of a simulated peripheral nerve block under ultrasound guidance, Sites and colleagues suggested that the number of attempts to achieve ultrasound-guided regional anesthesia (UGRA) proficiency may be relatively low (7). However, other studies using a simulated UGRA task have reached the opposite conclusion, that a greater number of attempts may be required with a high degree of individual variability (8,9). Even by the 60th block attempt, a novice learner may still commit an average of 2.8 errors per procedure (10).

Practice, Practice, Practice

In his book *Outliers*, Malcolm Gladwell presents the concept of the "10,000 hours rule" (11). According to Gladwell, "If you look at any kind of cognitively complex field, from playing chess to being a neurosurgeon, we see this incredibly consistent pattern that you cannot be good at that unless you practice of 10,000 hours, which is roughly ten years, if you think about four hours a day." In an article he wrote for The New Yorker, Gladwell asserts, "In cognitively demanding fields, there are no naturals."

This concept of deliberate practice in the development of expert performance has been studied in medical education and other fields by Ericsson and others (12-16). For regional anesthesia, one randomized study has compared simulation-based deliberate practice to self-guided learning and practice on residents' acquisition of UGRA skills (17). The results of this study do not show a difference in performance based on learning intervention, and residents in the self-guided group spent less than 15% of the time in training (17).

Accounting for Individual Differences

A limitation of many medical education studies is that they tend to assume that all learners learn the same way and do not account for individual differences that clearly exist (9). In a study by Shafqat and colleagues, the mental rotation test (MRT) was used as an assessment of visuospatial ability prior to studying performance of a simulated UGRA task (18). The results of the study show that those novice learners with high scores tend to perform better on the UGRA task when assessed using a global rating scale (18).

Technology for Teaching and Learning

The use of simulation has become ubiquitous in anesthesiology education (19), and there are several applications in teaching regional anesthesia (20). In a recent review, publications on simulation in regional anesthesia are broadly categorized into: 1) simulation-based educational interventions; 2) novel simulator designs; 3) use of the simulated environment as an experimental setting; or 4) other uses of simulation unrelated to the other three categories (20). Studies of simulation as an educational intervention for novice learners show mixed results in terms of effectiveness when compared to other learning modalities (20). However, there is face validity in training novices

first on part-task training simulators ("phantoms") for UGRA before attempting these invasive procedures on actual patients. These phantoms vary in design (21-23) but can be generally classified as inorganic and organic. Inorganic phantoms are commonly manufactured out of various types of gel mold, elastomeric rubber, or some other synthetic material; advantages include reusability, and disadvantages include inability to inject fluid and retention of previous needle tracks (20). Organic phantoms may involve non-living human cadaver or animal tissue specimens; advantages include sonographic realism and ability to inject fluid or air (24). and disadvantages include lack of reusability (20). The use of part-task training phantoms can also be combined with mannequin-based scenario simulation (referred to as "hybrid simulation") (25). In one of the first studies by our ADAPT (Anesthesiology-Directed Advanced Procedural Training) research group, we evaluated the effectiveness of a standardized training program using hybrid simulation (25). For this study, the subjects were anesthesiologists already in practice for 10 years of more but with no formal regional anesthesia or ultrasound training. In this population of learner, 8 hours of training including lectures, live model scanning, and simulation resulted in marked improvement in ultrasound-guided perineural catheter insertion performance from baseline (25). In addition to simulation technology for teaching, there have been innovations in device development to aid the learner in UGRA. Echogenic technology for needles and catheters are currently available and marketed to help anesthesiologists perform UGRA procedures efficiently and safely (26,27). Needle guidance systems have also emerged to aid the anesthesiologist with needle tracking and visualization (28).

Technology for Assessment

Despite multiple areas of technological development in teaching and learning UGRA, assessment remains technologically challenged. The most common methods to assess performance reported in published studies tend to be extremely labor intensive: video recordings of subjects during the performance of live or simulated procedures followed by painstaking review by one or more experts using a lengthy assessment scoring tool (10,25,29-32). Global rating scales contain fewer items for scoring and have been validated against more complex tools (33,34); however, they still require one or more reviewers either observing in real-time or retrospectively rating videos. None of these tools collects data directly from the person performing the procedure and thus cannot be considered truly objective. Hand motion analysis using the Imperial College Surgical Assessment Device (ICSAD) has been studied in the context of regional anesthesia for epidural placement and UGRA (35,36). Position sensors are attached to the operator's hands, and data are recorded during each phase of the procedure (e.g., scanning and needling for UGRA) (35). Use of the ICSAD has now been validated against both a multiple item assessment tool and global rating scale (35). One limitation of the ICSAD is that it is limited to mechanical performance and does not assess visual performance, an essential part of UGRA. Another new technology recently described for UGRA education is eye tracking (37). Eye tracking has been studied in other medical specialties (38-40) and offers the ability to "see" what the operator sees. The eye tracking system consists of a visor, computer, and software. Simultaneously, the system records the operator's visual field through an externally-facing camera and also tracks the operator's gaze using near-infrared illumination to create reflection patterns on the pupil and cornea (37). Although rigorous prospective studies have yet to be performed, eye tracking represents a potential tool to objectively assess visual performance during UGRA.

In summary, there is strong evidence to support the use of ultrasound in the practice of regional anesthesia. Learning UGRA requires specialized training which will likely differ based on the experience of the learner as well as individual differences in learning preference. Development of technology for teaching and learning currently outpaces technology for assessment with simulation now commonly integrated in various forms within UGRA education. Newer tools such as eye tracking for assessment are under investigation and may offer objective metrics of UGRA training milestones.

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ANESTHESIOLOGY 2017
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Professionalism in Your Daily Practice: A Case Based Review

Saundra Curry, MD **New York, NY**

In 2002 the European Federation of Internal Medicine, the American College of Physicians-American Society of Internal Medicine (ACP-ASIM) and American Board of Internal Medicine (ABIM) collaborated to write Medical Professionalism in the New Millennium: A Physician Charter[1]. This charter laid out three fundamental principles and ten commitments all which encompass the basis of medicine's contract with society. The ASA, the ABA and some 130 other societies worldwide have endorsed this charter, but there is precious little in the literature about how practitioners are and should be applying this charter to their everyday work lives. As yet there is no definition of professionalism that everyone agrees upon. Differing specialties view professionalism through their own eyes[2] which is appropriate since we all have different types of interactions with patients and colleagues. But professionalism in anesthesia is still not well defined, an unfortunate situation, because it impacts us at every level in our daily working lives. Each paragraph of the charter can be applied to what we do.

TENETS AND SCENARIOS

Principles

Principle of primacy of patient welfare: There can be no argument about the importance of this statement. We care for patients at their most vulnerable moments. They are ill, frightened, and for the most part, unconscious. We as anesthesiologists are patient advocates and protectors in operating room and critical care environments. Nothing should interfere with this duty to altruism.

Principle of patient autonomy: Again, we are protectors of patient rights. We have a duty to present the options patients have for their care and cannot force them to have any type of anesthesia. They rely on us to use our best judgment to provide the best of care, given the surgical situation. We can't force regional or general on them, but can only present the best options available to them. This also applies to DNI/DNR scenarios.

Principle of social justice: This principle may seem removed from the operating room, but in fact appears more often than one would think. We take all comers to the operating room, and should delegate care based *only* on the basis of the medical status of the patient, not their ability to pay, their standing in the community, or any other social characteristic.

Commitments

It is late at night and most staff have left for the day. A patient whose case has been delayed for hours presents for shoulder repair. Since it is late your plan is to anesthetize the patient using general anesthesia and an LMA. However, the patient and the surgeon are hoping for a regional technique. The patient is fearful of general and the surgeon is used to working with the regional team who would have placed some sort of brachial plexus block. You are not comfortable doing a block and in fact, you were supposed to attend a block workshop recently but have never found to the time to fit it into your schedule. You convince the patient and the surgeon that you will put in a block after he is asleep, because "it is better that way". After induction (the surgeon is not in the room) you just skip the block and tell the returning surgeon to proceed. After the case you tell the patient that "the block didn't work well" and promise him lots of pain medication to take home so he' be comfortable.

Commitment to professional competence: The decisions made over ten years ago to require recertification on a regular basis satisfies this commitment. And the recent changes to MOCA, requiring lifelong learning and maintenance of clinical skills show the world at large that we acknowledge that modern medicine is an ever changing field. Practicing with the skills learned long ago is not enough. Best practice requires keeping up to date in everything.

Commitment to honesty with patients: Lying to patients about their care can only lead to disaster. Medical errors need to be acknowledged so patients can be properly cared for. Patients suspect many things are done to them while under anesthesia that they don't know about and might not approve of. If students, vendors, etc. are going to be

around this needs to be agreed to ahead of time and then followed through. If a patient refuses this sort of contact, that wish must be honored. If it can't be, they must be told.

At a party recently you meet a man who seems vaguely familiar but you can't place him. The two of you hit it off instantly and you spend the entire party with him, drinking and enjoying yourself. You even find yourself telling a few patient "war stories" about life in your pain clinic since he seems fascinated by your work and flatters you with his attention. You end up dating this man for several weeks. He then appears in your pain clinic looking for relief from chronic back pain symptoms. He is only interested in opioid treatment as he says that's the only thing that works for him. You realize that you had treated him for this same back pain a couple of years ago but had passed him on to another partner when you went away on vacation and had not seen him since.

Commitment to patient confidentiality: No one wants to hear about their case in elevator discussions. Electronic media make this commitment even harder to adhere to. However, it again is our duty to protect our patients' medical information, which extends from the type of surgery they are having to their diagnoses and genotype.
Commitment to maintaining appropriate relations with patients: Exploitation of any sort by practitioners of their patients is wrong and cannot be tolerated.

As a member of the hospital Patient Safety Committee you are committed to helping improve certain practices around the hospital that have become problematic. Drug shortages have led to fights among specialties as to who should have priority over using certain critical drugs, the operating rooms, or the ICUs. To save money, refresher courses such as BLS and ACLS have been stopped at the hospital and everyone has been told to "get certified on your own", a difficult prospect. Your hospital is in a rural area with limited access to other ways to get certified. Online courses are good for theory, but not practical application. Along these same lines, clinic hours have been shortened to save money and many patients are finding they have to wait a long time for appointments. What can you as an anesthesiologist do?

Commitment to improving quality of care: Anesthesiologists have always been leaders in quality and safety. This extends from maintaining competence, reducing errors and collaborating with other specialties to optimize clinical outcomes.
Commitment to improving access to care: We need to strive to improve access to the best possible care that our patients can receive. This includes supporting efforts to improve public health, such as the ASA's initiative to stop smoking.
Commitment to a just distribution of finite resources: As anesthesiologists we can aid in this commitment by avoiding waste and applying the best cost effective care possible.

At a faculty meeting your chair announces that she has access to some funds to put to use in the department. The researchers have been clamoring for updating their facilities so they can continue some important initiatives not covered by their grants. The educators want the funds to improve the simulation center which has fallen into disuse because of being outdated. The clinicians want the lounge refurbished "for everyone's use". There is enough money to completely redo one of the projects but not all three. The chair is asking for input as to how to allocate the money.

Commitment to scientific knowledge: This commitment may be one of the easier ones for anesthesiologists to understand. Scientific research is the way our specialty will move forward. Not everyone is cut out to be a researcher, but we can all read about and apply the advances shown to be improvements to patient care. We can also support those who do research with time and money.

A surgeon with whom you work on a regular basis is telling you about a lucrative investment possibility. He and some other surgeons have developed a computer program that could revolutionize hospital EMR systems. He likes you so is offering to get you in on the ground floor. You look over the plans and are very impressed by what you read. The next week your chair tells you that the CEO of the hospital has asked that you be placed on the hospital procurement committee, the one that looks at new equipment and systems. You are flattered by this as it is a powerful committee and agree right away. Then you remember that the CEO is the brother-in-law of the surgeon who invited you to invest in the new EMR system the hospital is now reviewing.

Commitment to maintaining trust by managing conflicts of interest: Full disclosure is the only way to go with this commitment. Anesthesia is a specialty that draws clever people who are interested in new product and drug development and who also know how to pursue these interests to potential financial markets. We need their know-how, we and our patients just need to be clear that it is the *patients'* best interest that is being maintained, not just the bottom line of any new company.

A colleague has been going through some difficult times. His wife has been ill and his four young children are not dealing well with the absence of their mother. His normally even temper has snapped on a number of occasions in dealing with challenging staff at all levels. Surgeons have begun requesting that he not be assigned to their cases and he is starting to lose income as a result. You have been friends with your colleague but you are actually enjoying the increase in prestige and income that you have been getting as a result of your friend's misfortunes. He calls you up one day asking for help.

It has been a long case and a patient having abdominal surgery has had several turnovers of staff. Now that the case is finishing you think a TAP block would be perfect for pain control in this patient and the surgeon agrees. However, there is no documentation that consent was obtained for this procedure at the beginning of the case. How do you proceed?

Commitment to professional responsibility: This final commitment encompasses many duties, including promoting the specialty, maximizing excellent patient care, self-regulate, respect one another, set educational standards, as well as support organizations that promote the specialty on a national level. Much of how we practice can be mandated at a national level and we need to be involved in those processes.

ADVERSE CONSEQUENCES TO PATIENTS

What happens if we don't adhere to the principles and commitments? The consequences of *not* adhering to these tenets may be easier to see than their daily application.
Patient welfare can be easily compromised if their best interest is not placed paramount. We could leave patients alone under anesthesia. Anesthesia is so safe these days nothing would happen, right?
Patient autonomy is paramount. As an example, the DNR debate over the last 20 years has shown that patients want their rights acknowledged and respected. Not to do this leads to patient mistrust and potential law suits.
Social injustice gives good care only to those who can afford it or to those we happen to like because of their race, ethnic background, religion, or political affiliation.
Professional incompetence means that your colleague who hasn't read a journal or attended an educational meeting for the last ten years might be giving you anesthesia in an emergency. Or perhaps he has a substance abuse problem…
Dishonesty with patients means that if a mistake was made and not reported, the mistake may be repeated (drug reactions) or the patient may not get the appropriate care to rectify the new problem.
Lack of confidentiality - means that the world can hear about a patient's issues. This can lead to job consequences, marital discord, and other topics that are none of anybody else's business.
Inappropriate relations with patients can lead to wrong care, bullying, and professional blackmail.
Not improving the quality of care means we are taking care of today's problems with yesterday's solutions. This may work for a while, but is doomed to failure eventually.
Not improving access to care means we end up having to care for sicker patients than we have to. If they don't have access to good primary care, our job is that much more difficult.
Unjust distribution of finite resources means that those who need care the most won't get it when they need it.
Lack of scientific discovery - means that we never advance the specialty and cannot improve patient outcomes.
Not managing conflicts of interest means that we lose the public trust. This is another form of altruism where the public needs to know that we are putting their needs above our own, not vice versa.
Not taking professional responsibilities seriously means no one else will either. If we don't care enough to support our major organizations as they fight for our rights in Congress, for example, why should Congress listen?

PERSONAL AND DAILY APPLICATIONS

Swick et.al.[3] point out that one of the flaws of the Charter is that it concentrates on duties and not on values that are virtue based. Their theory is that duties without values are very hard to stick to and one needs to absorb. Virtues have the benefit of being inherent in people and not externally driven. Therefore they have better chance of sticking. The other important benefit is that virtues are what people bring to any situation regardless of the context. The operating rooms are inherently stressful with different groups of people working together. Each has their own agenda. If everyone concentrates on the patient as being the key element that has brought them all together, focus can be maintained on the only important person in the room. One of the common grumbles of anesthesiologists is that they don't get enough respect from surgeons and nursing staffs or even patients. Respect is earned, not automatically granted. It is true that patients do not come to the hospital to get anesthesia. Surgeons bring them in so there is an inherent dichotomy for everyone to deal with. However, it is unlikely that patients would come for surgery if they thought they were not getting any of the services we provide, i.e., analgesia, amnesia, and maintenance of life. Lesser et.al.[4] bring up a slightly different emphasis. They focus on behaviors of individuals and organizations because attitudes (values and virtues) are very hard to adjust. Behaviors are teachable, learnable and can be assessed. Quoting Aristotle, *"Excellence is an art won by training and habituation. We do not act rightly because we have virtue or excellence but rather we have those because we have acted rightly. We are what we repeatedly do. Excellence then is not an act but a habit."* It is virtually impossible to change other people. One can only work on oneself.

Leape et al [5,6] looked at disrespectful behavior and noted how sort of behavior can seriously disrupt the work environment. Making patients wait unreasonably for appointments is disrespectful to them. Demeaning behavior to a nurses and ancillary staff is disrespectful. Abuse of residents, students and colleagues is disrespectful. All of these can threaten patient safety by impacting collegiality and cooperation essential to teamwork.
Yet thinking of professionalism as a list of duties or values or even specific behaviors does not really get to the point. Wynia et al[7] noted that what is needed is a foundational understanding of what professionalism is all about. The behaviors and lists created are derivative of the belief system of professionalism. Professionalism is the motivational force that brings practitioners together to create and keep shared promises to the public. It ensures that practitioners are worthy of patient and public trust. With professionalism as a belief system it becomes clear that technical, interpersonal, communication, and knowledge skills are all interlocking promises that are what professionalism is all about. True professionalism requires practitioners to work together across specialties and divides to insure the promises to patients are kept. But it begins with individuals, us, to ensure that these promises are kept. If we as individuals believe in professionalism and work individually and together to ensure the best for our patients, we will gain the respect of our patients and colleagues alike. We will also be taken quite seriously as patient outcomes improve and burnout among practitioners decreases. As so eloquently laid out in the March 2016 ASA Monitor[8], "Without professionalism, the other core competencies simply lack effectiveness."

Here's an approach that encompasses the some of the tenets of the Charter, includes personal virtues and behaviors.
I will place patient welfare above all else. I will have carefully planned my anesthetic for the case at hand, having discussed the surgeon's needs with him/her ahead of time. I will discuss plans and goals with the patient at a level
I will listen to the patient. Their concerns and desires are important in my plan for how I care for this patient. I will show them compassion for their concerns. I do this every day but this may be the patient's first encounter with the OR's.
I will give them the best care, regardless of their place in society.
I will strive for excellence in my profession, not just competence. That means that every day there is something to learn and improve upon. My board certification was just a large stepping stone in my drive to become an outstanding and expert clinician. Lifelong learning and professional development will be my tools.
I will be honest in my dealings with all maintaining integrity and accountability. This includes, patients, OR staff, surgeons and consults. Honesty about mistakes, errors in judgment, as well as thoughts on chances of success in a particular procedure will gain me the confidence of those with whom I work. I will also honor myself and not abuse myself with drugs, lack of sleep, etc which may compromise my ability to care for my patients.
I will maintain the confidentiality of my patients and thus they will know they can count on me.
I will maintain strictly appropriate behavior with my patients.
I will take my professional responsibilities seriously. This includes supporting my national organizations who speak for me to the public. But it also means treating colleagues of all specialties with the respect I expect from them. I will confer with my surgical colleagues about upcoming cases so that an appropriate care plan can be

established. If I suspect a colleague in any specialty is behaving inappropriately (drugs, alcohol, behavior) I will make sure it gets reported to the appropriate authorities. This shows compassion for the person and care of any patients that may be in harm's way.

Ultimately by adhering to these duties, virtues and responsibilities and *acting* on them we will earn the respect of all with whom we work, take great care of our patients and honor our specialty and ourselves. Issues in professionalism are here to stay.[9] Surgeons are already on the bandwagon in their teaching of residents.[10] We need to get a head start in our profession by adhering to these tenets now.

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8 Pages Maximum

ANESTHESIOLOGY 2017
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Palliative Care 101

Kristin D. Forner, MD — **Asheville, NC**
Allen N. Gustin, MD, FCCP — **Chicago, IL**

Palliative care has been defined as patient- and family- centered care that attempts to optimize quality of life while minimizing the burden of disease. Palliative care is provided by a team of interdisciplinary specialists who address the physical, emotional, psychosocial and spiritual domains that make up a whole person. Unlike hospice care, palliative care is not constrained to any expected prognosis, so patients may receive palliative care at any stage in the course of their serious illness and they may receive curative treatment alongside palliative treatment. Palliative care is compatible with patients in both the perioperative and the critical care settings.[1]

From its inception, the field of palliative care has focused on the importance of patient-centered care and shared decision-making, and multiple studies have demonstrated that palliative care provides better quality care at lower cost.

When palliative care teams become involved, patients' symptoms are better discovered and managed, and they experience reduced health care expenditures, better achievement of their care goals and – in some illnesses – improved survival.[2345]

There are 30 million major inpatient surgeries and 50 million ambulatory outpatient surgeries in this country every year. More than half of hospital admission expenses are related to surgical care, and almost a third of patients 65 years and older undergo surgery the year before they die. The number of surgical patients 65 years and older is expected to reach 55 million by 2020 and 72 million by 2030.[6] Approximately 15% of patients with DNR orders come to operating room (OR) for a procedure aimed at improving quality of life (QOL).[7]

Best Practice Guidelines recently issued by the American College of Surgeons' National Surgical Quality Improvement Project and the American Geriatric Society for Optimal Preoperative Assessment of the Geriatric Surgical Patient recommend that, in the preoperative visit setting, providers:

- Determine patients' treatment goals and expectations
- Consider these goals in the context of possible treatment options, and
- Place advance directives and healthcare surrogate or HCPOA information in the medical chart

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[1] National Hospice and Palliative Care Organization website. http:// www.nhpco.org/. Accessed August 17, 2015.
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If there is no preoperative visit, and instead patients are arriving to the OR in an emergency, the American College of Surgeons' (ACS) guidelines recommend that most patients receive aggressive care during this initial phase of their treatment as outcomes here are most favorable, but that conversations around treatment goals occur shortly thereafter and are revisited as often as these patients' care warrants.

With regard to perioperative code status conversations specifically, the ACS, the American Society of Anesthesiologists (ASA), and the Association of peri-Operative Nurses (AORN) propose a "required reconsideration conversation." In 1993, the ASA formally recognized the need for a "required reconsideration conversation" when a patient with a Do Not Resuscitate (DNR) order needs to go to the OR. The guidelines were then updated in 1998 and give a more goal-directed approach to perioperative DNR orders. This is all in an effort to support a patient's right to self-determination. There are three options for changing a DNR order perioperatively, and the ACS and ASA are in agreement about these options:

- Full Attempt at Resuscitation
- Limited Resuscitation Based on Particular Procedures, or
- Limited Resuscitation Based on Patient's Values and Goals

If the patient asks the anesthesia provider to use his/her clinical judgment to determine when a resuscitative procedure is appropriate, further exploration of the patient's goals and "minimally acceptable QOL" should follow.

At minimum, according to all three of the aforementioned professional societies, perioperative code status conversations should include:

- A review of the existing DNR order and clarification of its intent
- A discussion about any exceptions to the order should complications arise
- A discussion regarding the plan for reinstating the DNR order should it be postponed perioperatively, and
- Documentation of the conversation[8]

Patients with serious illness and poor prognoses often receive care that does not help them achieve their goals. While not an exhaustive list, below are a few examples where palliative care could significantly improve standard perioperative care:

- The elderly – especially those with dementia – and their families could benefit from thorough preoperative goals-of- care conversations. These patients are also at highest risk for postoperative delirium. Are the procedures we providers recommend going to give these patients what they want and need?
- Patients with cancer who have chronic cancer-related pain, and who are on opiates preoperatively, may require a more complicated pain management regimen perioperatively. These patients may also benefit from goals-of-care conversations.
- End-stage heart failure patients who are being evaluated for mechanical assist devices need more thorough preparedness planning than a simple advance directive or living will provides. The Joint Commission now requires a palliative care provider to be a part of the core interdisciplinary ventricular assist device team for programs to receive advanced certification.
- Patients with multiple comorbidities are often symptomatic preoperatively and could use palliative care involvement to optimize their symptom management throughout the perioperative period.
- All patients receiving a tracheostomy and/or a feeding tube deserve a goals-of-care conversation to ensure these procedures are in line with patients' and family members' expectations.
- And patients, and families of patients, who have suffered neurologic or orthopedic trauma may need the kind of emotional support or goals-of-care guidance palliative care teams are trained to provide.

Even though most anesthesiologists are not formally trained in palliative care, each is inherently an excellent physician experienced in the art of palliation of the symptoms to pain, nausea/vomiting, and anxiety/agitation. All

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anesthesiologists are capable of providing primary palliative care. Primary palliative care is defined as the basic communication and management "skills and competencies required of all physicians and other healthcare professionals" who care for patients with serious illness.[9]

Anesthesiology, as a field, provides a few avenues where quality primary palliative care could make an extraordinary difference for this patient population. There are four areas, in particular, where our skillset can be uniquely critical:

- Interventional pain management
- Sedation near the end of life
- Discontinuing mechanical ventilation
- Organ donation

Anesthesiologists receive unparalleled education and training in analgesic and sedative pharmacology and titration, and procedural interventions for pain management. We care for critically ill patients every day. We regularly treat patients for anxiety and agitation and help them cope with their new illness-related realities. We are airway experts and thus intimately know how to comfortably intubate and extubate patients. And when patients have agreed to donate their organs, we are the ones who are called to transport them to and care for them during their very last breaths. By better understanding which patients can benefit from palliative care, and by becoming more competent in facilitating conversations around patients' goals for their care, anesthesiologists can play a major role in helping patients receive better care.

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ANESTHESIOLOGY 2017
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ALGORITHMIC APPROACH TO LOW BACK PAIN

Nagy Mekhail, MD, PhD

ANATOMIC CONSIDERATIONS:

The lumbar spine plays an instrumental role in locomotion and posture. The intricate anatomy of the lumbar spine is a remarkable combination of five strong vertebrae, multiple bony elements linked by joints, ligaments, and tendons, large muscles, complex innervations and vascular supply.
A typical vertebra consists of a vertebral body joined by pedicles to the posterior elements, namely the laminae, superior and inferior articular processes, transverse processes, and the spinous process. The top and bottom of each vertebral body is "coated" with an endplate. The endplates of the vertebral bodies are joined to one another by an intervertebral disc and help support the disc.
Intervertebral discs consist of a central gelatinous nucleus pulposus composed of water and proteoglycans. The nucleus pulposus is surrounded by the annulus fibrosus. The inner portion of the annulus is composed of fibrocartilage, whereas the outer fibers are made of concentrically oriented lamellae of collagen fibers. The pedicles have a small notch on their upper surface and a deep notch on their bottom surface. These superior and inferior vertebral notches that are located above and below the pedicles form the intervertebral foramen, where the nerve roots exit the spinal canal. The spinous process extends posteriorly from the point where the two laminae join, and acts as a lever to effect motion of the vertebra. The 4 articular processes link with the articular processes of adjacent vertebrae to form facet joints. The lumbar facet joints form the posterolateral articulations connecting the vertebral arch of one vertebra to the arch of the adjacent vertebra. Each facet joint receives dual innervation from medial branches arising from the dorsal ramus at the same level and the medial branch of the nerve one level above the facet joint. The lateral recess is the space within the spinal canal located toward the sides. Anatomically, the lateral recess is bordered laterally by the pedicle, posteriorly by the superior articular process, and anteriorly by the posterior lateral surface of the vertebral body and adjacent intervertebral disc. The thecal sac forms the medial border of the lateral recess. Age-related changes in bones, facet joints, ligaments etc. may cause these structures to encroach on the lateral recess, creating a condition known as lateral spinal stenosis.

For the sake of providing a comprehensive yet simplified approach to the most common low back pain problems, will divide the lumbar spine into three compartments and address the pain generators in each compartment.
The anterior column is composed of:

- Anterior longitudinal ligament
- The vertebral body and intervertebral disc

The middle column is composed of:

- Posterior longitudinal ligament
- The spinal canal with all its contents

The posterior column is composed of:

- Spinous process
- Pedicle
- Lamina
- Facet joints
- Interspinous ligament
- Supraspinous ligament
- Ligamentum flavum

THE ANTERIOR COMPARTMENT

The anterior compartment is both the largest and strongest of the three spinal compartments, and is comprised of the bony vertebral bodies and intervertebral discs. These elements are bounded ventrally by the anterior longitudinal ligament and dorsally by the posterior longitudinal ligament. The center of gravity passes through the center of the anterior compartment supporting a majority of the weight of the head, upper body and trunk. Despite its large volume, the anterior compartment contains few structures, and pain complaints originate primarily from pathology within either the bony vertebral body or the intervertebral disc.

DISCOGENIC PAIN

Discogenic pain can be defined as pain that results from irritation of the nerve receptors located in the annulus fibrosus; most commonly caused by internal disc disruption/derangement (IDD). Pain arising from IDD in the lower lumbar segments can be mistaken for radicular pain since both etiologies have symptoms which can radiate to one or more lower extremity dermatomes.

Diagnosis

There are no widely accepted diagnostic criteria for low back discogenic pain. Typical characteristics include continuing pain in spite of conservative treatment, for six months or longer that is localized to the medial aspect of the spine. Discogenic pain typically worsens when performing activities that result in an increased intradiscal pressure such as sitting or loading maneuvers, and is improved with recumbency. Although discogenic pain might radiate to the buttock, thigh or leg, but such radiation does not follow the typical radicular distribution as the in radiculopathy secondary to herniated nucleus pulposus (HNP). The neurologic exam is usually normal and provocative straight-leg raising maneuvers are negative differentiating this condition from lumbar radicular pain syndrome. Physical exam maneuvers aimed specifically at provoking discogenic pain are non-specific.

Imaging modalities can help suggest IDD when an annular tear is present, and may be supported by the presence of a high intensity zone (HIZ) on MRI. Nerve root compression is usually absent. Despite the ability of MRI to visualize disc degeneration and quantify disc height, degenerative MRI findings are frequently seen in asymptomatic people and so such findings cannot be used solely to diagnosis IDD.

Although discography remains a controversial test yet, if properly administered, it yields very valuable diagnostic information. Contrast is introduced into the nucleus pulposus under pressure to describe the disc morphology, visualize annular fissures that might be contained or communicating with the epidural space and elicit pain that is concordant to the patient's discogenic pain. The procedure is performed in the lightly sedated patient at a minimum of two contiguous levels with the second level serving as a control. Manometry measurements during the procedure provides the basis for interpretation. A chemically sensitive disc will generate concordant pain at <15psi above opening pressure following injection of <1ml of contrast. A mechanically sensitive disc will generate pain between 15-50psi above opening pressure, while pain generated between 51-90psi represents an intermediate response. Lack of a pain response at pressures greater than 90psi is considered normal. It is important to note that a positive test result is one that reproduces pain similar in character and location to the patient's typical pain, while the adjacent discs are pain free. A CT is then performed to show images supporting the pain distribution findings.

The diagnostic discogram can be followed with a functional assessment post-procedurally by injecting 0.5ml of local anesthetic into the painful disc through a tiny plastic catheter left within the nucleus pulposus. Following recovery from sedation, the patient is instructed to perform those activities, which provoke their typical pain, and if both patient-reported and functional assessments shows improvement of pain and function after injecting a very small volume of local anesthetic into

the nucleus pulposus, the diagnosis of discogenic pain is confirmed. Despite the promising initial results of identifying as high as 38% false positive provocative discogram, functional anesthetic discography has not been adopted in clinical practice.

Treatment

Conservative options for discogenic pain are limited and lack a large quantity of supporting evidence. NSAIDs and acetaminophen/opiate combinations are often employed as first line agents for symptomatic relief. Physical therapy, bed rest and spinal manipulation were shown to be ineffective modalities in a systematic review.

A number of non-surgical interventional procedures have been either adapted or developed for the treatment of discogenic pain using heat including intradiscal radiofrequency ablation, intradiscal electrothermal therapy (IDET) and biacuplasty. Injection of intradiscal corticosteroid following positive discography does not consistently improve pain outcomes. Similarly, radiofrequency ablation of the nucleus pulposus using equipment adapted from radiofrequency neurotomy procedures or with the disctrode system has not consistently resulted in significant improvements in pain scores or functional improvements.

IDET also known as intradiscal electrothermal annuloplasty (IDTA) requires placement of an electrothermal catheter along the posterior border of the junction between the nucleus pulposus and the annulus fibrosus. The intradiscal portion of the catheter is heated with the likely mechanism resulting in ablation of the aberrant nerves thought to be responsible for generating discogenic pain. Although there were good amount of supportive trials, IDET is no longer part of clinical practice due to the initial over utilization which led to lack of reimbursement by health care payers.

Intradiscal biacuplasty was developed to address the technical challenges of IDET and offers several advantages. The procedure entails placing bilateral intradiscal electrodes within the posterior aspect of the disc. The bilateral probes create a uniform band lesion along the posterior wall of the disc at lower temperatures and for shorter duration than IDET. A randomized sham-controlled study provided statistically significant data showing that biacuplasty helped reduce pain, lessen disability and improve overall physical functions at the 6-months follow-up interval. Additionally, although both randomized groups did not demonstrate any statistical difference, the treated group did report a considerate reduction in opioid intake (42). In a follow-up study, treated patients were followed at the 9 and 12 months interval and showed maintained improvement post-procedure. Sham patients were also given the opportunity to cross over and receive treatment. Their results supported the previous findings of improvement of physical functions, reduction in pain and patients were less disabled at 6 months (41).

More invasive forms of treatments that have recently been introduced and are currently being investigated for further evidence include spinal fusion and artificial disc replacements. Complications of the former have been avoided by implementing the latter which involves lumbar disc prosthesis at the levels thought to be inducing the pain. The benefits of this is that the patient can still have a large extent of spinal motion while preventing further degeneration at adjacent levels. However, due to the invasive reality of the procedure, large scale studies have yet to be carried out (23).

Lastly, a new promising minimally invasive procedure, the intradiscal methylene blue injection, is currently giving promising results. Two recent studies reported satisfactory results with minimal complications. The methylene blue is thought to alleviate the pain by destroying the nerve endings that are causing the discogenic pain and reducing inflammation at the levels of degeneration of lumbar discs (24, 25).

DISCITIS AND VERTEBRAL OSTEOMYELITIS:

Discitis and vertebral osteomyelitis are additional etiologies of anterior compartment spine pain, and are considered collectively since the pathophysiology and treatment are complimentary; with the one exception that discitis may be a result of an autoimmune disorder. Rates of both discitis and vertebral osteomyelitis are increasing likely due to a combination of the increased use of injectable drugs, increasing age of the population and increasing incidence of nosocomial infections. Intervertebral discs become infected due to spread from the adjacent vertebral bodies and since they have no blood supply it is difficult to treat them with IV antibiotics.

Diagnosis

Discitis and vertebral osteomyelitis present as axial back pain that worsens at night. Fever is not a universal finding and its absence should not exclude the possibility of an infectious etiology. Tenderness to palpation over the effected segments is a sensitive, but not specific, clinical indicator. Acute phase reactants including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are of great value as prognostic indicators. Blood cultures are positive in a small majority of patients and should be obtained since positive cultures can guide therapy and can limit the need for further diagnostic workup.

Plain radiographs are initially normal within the first two weeks of presentation, but destructive changes in two contiguous endplates and collapse of the intervertebral body can occur with progression. Rarely are two adjacent vertebrae involved with the presence of a normal intervertebral disc, and if observed, should prompt investigation into another diagnosis such as malignancy or fracture.

Magnetic resonance imaging (MRI) is the most sensitive imaging modality to detect osteomyelitis. T1 weighted MRI findings consistent with osteomyelitis include signal loss in the vertebral endplate and decreased signal intensity in the vertebral body. Discitis is seen on T2 imaging as increased signal intensity within the disc. Triple phase bone scan is an alternative radiographic modality that has high sensitivity, but is indistinguishable from vertebral fractures. Surgical biopsy can be performed when blood cultures do not implicate a causative organism and the response to standard antimicrobial treatments has failed.

Treatment

The primary goal of therapy is to eradicate the offending organism and limiting the spread of the infection. Staphylococcal, streptococcal and gram-negative bacilli are the most often causative agents and empiric antimicrobial therapy against these organisms are often employed while awaiting microbial cultures. Morbidity and mortality are reduced when antimicrobial therapy is introduced shortly after initial presentation. Duration of therapy tends to be long, and may necessitate the use of parenteral antimicrobials if an agent is isolated which is not sensitive to oral therapy. An analgesic regimen is often required with the goal of improving mobility and restoring functional status. Surgery may be required in those patients with progressive disease unresponsive to antimicrobials, those with cord compression or with the presence of coexisting abscess. In autoimmune causes of discitis, treatment of the underlying autoimmune disease would be the primary focus.

VERTEBRAL COMPRESSION FRACTURES:

Vertebral compression fractures (VCF) are a common cause of back pain in the elderly population with a 25% lifetime incidence in postmenopausal women and an estimated 40% incidence in those over the age of eighty years. 700,000 VCFs /year occur as consequence of advanced osteoporosis, though neoplastic and traumatic etiologies are also, to a much lesser extent, implicated. Often as important as the fracture and associated pain, is the disability and social withdrawal which develops as a consequence of the VCF. Sequelae of VCFs include venous thromboembolic disease, progressive muscle weakness, restrictive lung disease and increased likelihood of nursing home admission.

Long-term bed rest after VCFs result in accelerated bone loss and increases in both morbidity and mortality.

Diagnosis

A history supporting VCF can vary widely, but often includes discrete onset of acute back pain after lifting or bending. It is estimated that two-thirds of VCFs pass undiagnosed, hampering early interventions to interrupt the sequelae of immobility which rapidly develop. A vague history in those patients who seek medical intervention for back pain complaints can be inadequately assessed and incorrectly attributed to worsening of chronic arthritic spine pain complaints precluding early intervention.

VCFs occur most often at the T12 or L1 levels due to the transition of the rigid thoracic zygapophyseal architecture to the more mobile lumbar spine. Subtle height loss and kyphosis can develop in those patients affected with VCF. Typically VCF results in at least 1cm of height loss, but height loss of >6cm was 94% specific to diagnose VCF by measurement alone. Because 19% of patients with a VCF will suffer a subsequent VCF within one year, recognition and early intervention is important. The risk of developing subsequent VCFs increases exponentially with a five-fold increased incidence after a single VCF, twelve-fold increase after two VCFs and a 75-fold increase after three or more VCFs in patients with persistent low bone density.

Lateral spine radiograph of the thoracolumbar spine is recommended as the initial diagnostic imaging modality when considering the diagnosis of VCF. Anterior wedge shaped deformities are most characteristic, and can be associated with vertebral end plate changes. MRI is the definite advanced diagnostic imaging modality of choice. MRI helps identify the age of the VCF with acute fractures demonstrating characteristic bone marrow edema. MRI adds the additional benefit of determining the integrity of the posterior wall of the vertebral body if an interventional approach is planned. CT scan provides a good assessment of the bony architecture and can be substituted in those patients with contraindications to MRI.

A musculoskeletal and neurologically focused physical exam should be performed to exclude cord compression, infection or other etiologies that may necessitate an urgent surgical consultation. Laboratory analysis is typically obtained by the primary care provider upon diagnosis and may include assessment of serum calcium, phosphate, 25-hydroxy Vitamin D levels and advanced tests to evaluate bone density include dual energy X-ray bone densitometry (DEXA scan) or quantitative computed tomography. Laboratory analysis is also useful if malignancy is suspected by clinical history, and may include complete blood cell count, erythrocyte sedimentation rate or protein electrophoresis.

Treatment

Initial management should be directed toward providing analgesia and resuming function to decrease the sequelae of immobility including venous thromboembolic disease, restrictive lung disease and mood impairments. No randomized controlled trial has demonstrated the superiority of one class of analgesic agents over another in the treatment of VCF, and selection of an agent is dependent upon the patient's comorbidities. The use of non-steroidal anti-inflammatory agents (NSAIDs) is somewhat controversial due to the uncertain effects of these agents on bone healing when studied in long-bone fractures. Many will chose to use a combination of opiate and acetaminophen to assist with the acute pain of a VCF, and avoid any potential increased risk of non-union. If osteoporosis is the etiology of the VCF, specific assessment and treatment of bone density should commence shortly after diagnosis. Optimization of calcium supplementation and antiresorptive therapies remains an important aspect of the VCF treatment strategy.

Although the effectiveness of back bracing has been studied prospectively in traumatic vertebral fractures and decreases in both pain and disability scores was demonstrated, caution should be exercised if a brace is provided to ensure that the device is to be used only temporarily for

symptomatic relief and should not be used to foster immobility. It is worthwhile to note that with each week of bed rest, the osteoporotic patient can lose up to 2% of their bone mass.

Deciding upon proceeding toward interventional treatments should be individualized based upon patient comorbidity and level of disability. When assessing the natural history of patients with osteoporotic VCFs, the majority achieved pain relief after three months with conservative treatment alone, though no predictors of those who would fail conservative treatment were identified.

VCF can be treated percutaneously on an outpatient basis with both kyphoplasty and vertebroplasty. Large-scale retrospective studies have associated percutaneous vertebral augmentation with a 37% decrease in mortality when compared to those in the conservative treatment arm. Vertebral augmentation has been shown to offer short-term pain relief, limit or reverse the local kyphotic deformity and increase functional capacity. Kyphoplasty offers advantages including restoration of vertebral height and a decrease in the local kyphotic angle, but is more costly than vertebroplasty and the importance of restoring vertebral height has not been quantified. The effectiveness of kyphoplasty is most pronounced at one-month follow-up, but improvements in treated populations have also been sustained at two-year follow-up. The most notable potential risks with vertebral augmentation include local cement extravasation and cement embolism, which are claimed to be less with kyphoplasty versus vertebroplasty.

The Middle Compartment

Lumbar spinal stenosis

Lumbar spinal stenosis (LSS) functionally impacts significant numbers of Americans per year. Current estimates place the number of Americans suffering from elderly lumbar spinal stenosis at 400,000. 47% of patients ranging from 60 to 69 years of age have mild to moderate stenosis and 19.7% have severe stenosis. LSS is becoming major health-care issue as the population ages. Although LSS is not life threatening, it can cause substantial disability with limitations to performing daily activities, and thus, the associated negative impact on quality of life (QOL).

The pathophysiological changes of Lumbar spinal stenosis (LSS) are caused by degenerative changes of the lumbar spine including thickened and buckled ligamentum flavum (LF), osteophyte formation, facet hypertrophy, and bulging of the intervertebral disk. This usually leads to narrowing of the central spinal canal with compression ischemia of the cauda equina. In a study of 191 symptomatic patients; LF hypertrophy was found to be the key contributor to their LSS (13).

Schonstrom et al, 1989 studies the changes in the dimensions of the lumbar spinal canal under both flexion-extension and axial compression-distraction using computerized tomography (CT) scans in human cadaver lumbar spine specimens. The cross-sectional area of the spinal canal was reduced by 16% (around 40 mm) when the lumbar spines were moved both from flexion to extension and from distraction to compression. An analogous decrease in the midsagittal diameter of the canal of 2 mm was found. During these motions, LF did not appear to be a significant factor for the dynamic changes affecting the dimensions of the canal (11, 12).

Diagnosis

Patients classically present with low back pain that may be associated with neurogenic claudication; described as pain radiating to the lower extremities that begins and worsens as the patient ambulates or stands and is relieved with flexion of the spine and sitting down. Neurogenic claudication is believed to result from structural narrowing of the vertebral canal that impedes venous return causing venous hypertension resulting in arterial ischemia of the cauda equina.

Imaging studies include standing AP, lateral, and flexion-extension lumbar spine radiographs to rule out spondylolisthesis. Plain films can show degenerative processes including disc degeneration,

osteophytes and facet hypertrophy. The gold standard imaging modality is MRI. T2 weighted MRI scans allows noninvasive evaluation of central canal stenosis. In cases where MRI is contraindicated or inconclusive, CT scan can directly view the effects of disc pathology, facet hypertrophy and buckled LF on the cross sectional area of the canal. The poor soft tissue contrast of the CT, that may impose difficulties in delineating the disc/thecal sac/LF interfaces, can be overcome by the addition of intrathecal myelography contrast. This provides excellent spatial and soft tissue resolution. Furthermore, it allows a dynamic imaging component.

Standing views in flexion/extension can demonstrate the reduction of the cross sectional area of the dural sac. Earlier studies used AP diameters of the dural sac to determine the degree of stenosis. 10 mm was considered absolute stenosis and 12 mm was suggestive of severe stenosis (30). In patients with dural sac area of less than 110 mm^2 on one or more levels that illustrate the clinical signs and symptoms of lumbar stenosis, MRI or CT myelography with axial loading is recommended (26). Additionally, MRI scans allow accurate measurement of the thickness of LF.

In recent studies, the use of electromyographic paraspinal mapping has been used to confirm the diagnosis of degenerative lumbar spinal stenosis in patients with mild to moderate symptoms. No specific technique is currently utilized, however, the procedure generally involves the placement of multiple electromyographic needles in different directions, while measuring changes in the electrical activity of the paraspinal muscles (27, 28).

It is important to differentiate neurogenic claudication due to LSS from radicular pain due to lumbar disc herniation or from intermittent claudication due to vascular ischemia. The latter may be mistaken for lumbar spinal stenosis because both conditions are associated pain that is exacerbated with exercise.

While vascular claudication diminishes with rest whether standing or sitting, neurogenic claudication often persists with standing still in an erect posture, but can only be relieved by assumption of stooped, flexed posture, or with sitting. Lumbar disc herniation may be associated with radicular pain similar to the neurogenic claudication that is worse with walking and standing. However, the pain is usually unilateral, rarely bilateral, but localized to the distribution of the affected nerve root(s) and will not be diminished with flexion of the spine nor will it be intensified with extension of the spine.

Treatment

Current therapeutic options range from conservative management to invasive spinal surgical decompression with lumbar fusion and with or without instrumentation. In between there are multiple minimally invasive and microsurgical options.

Conservative therapy versus surgery

Conservative methods of therapy may be of use in early to moderate cases, once patients progress to the point of moderate symptom severity, conservative methods may become ineffective or unrealistic.

Surgical decompression is shown to be helpful in about two thirds (2/3) of patients, but is associated with considerable morbidities (10). Patients who delay surgery have similar outcomes to patients who proceed immediately with surgery. Thus, the consideration of proceeding with surgery may await evaluation of comorbidities as well as assessing the patient's response to conservative therapy.

In a systematic review of the randomized controlled study comparing conservative and surgical approaches, the advantage of surgery was evident at 3 to 6 months and was maintained for up to 2 to 4 years. Nevertheless, the differences tended to be smaller beyond the four years.

Conservative therapy

Current recommendations for conservative treatment are based on empiric evidence and expert opinion. Additionally, there are no comparative trials of conservative therapies versus the natural history of spinal stenosis. Many studies do not specify the type of conservative therapy that is prescribed to the patients. Multidisciplinary treatment programs including physiotherapy, behavioral therapy, epidural steroid injections and a back exercises program have been recommended but not specifically validated. Lumbosacral corset, in a recent study, proved to be helpful in increasing walking distances and decreasing pain (29).

Physical Therapy

Physical therapy is a recommended treatment of neurogenic claudication; but its role has not been established with current evidence. It is uncertain which exercises constitute as effective exercise programs. Flexion-based exercises (e.g., stationary bicycle and inclined treadmill) increase the cross sectional area of the spinal canal and improve the microcirculation of the neural elements. These allow patients to tolerate the exercise program better and help improve weight loss and cardiovascular fitness. Aquatic therapy is also useful; it stretches the hip flexors and hamstrings and strengthens the abdominal and trunk muscles.

Interventional pain management options

Caudal epidural steroid injections produced significant reduction in reported pain and disability scores in 60% of patients trialed. Similarly, other studies have shown that both caudal and interlaminar lumbar epidural steroid injections were associated with improved function and decreased opioid intake. However, the benefits are usually short-term, lasting about 2 weeks to 6 months, with gradual decrease in efficacy with time (32). Use of contrast-enhanced fluoroscopy to guide epidural steroid injections is highly recommended, ensuring accurate medication administration (31).

Surgical Options

While early and milder cases respond to conservative measures, moderate and severe LSS may fail to sustain an adequate long-term relief and thus progression to the next option, which conventionally used to be open surgery, was inevitable in some patients.

Open Surgical Decompression

The wide variety of open surgical procedures developed to treat lumbar spinal stenosis has in some ways complicated the ability to clearly analyze outcomes as well as complication rates, and it is partly for this reason that such wide ranges of outcomes have been reported in the literature. Historically lumbar laminectomy, either hemi or bilateral laminectomy, or more extensive decompression with fusion has been the standard of care for surgical management of lumbar spinal stenosis. Obviously these surgical options were associated with extensive degrees of tissue trauma, hospital stay, longer recovery times and a long list of other potential complications.

Outcomes and Complications of Surgery

In a meta-analysis of surgical lumbar decompression literature by Turner et al, the average improvement in pain and mobility was reported as 64%, while others showed deterioration in the results over time. Late deterioration was thought to be due to compromising the stability of lumbar spine structures by wide open-surgical laminectomy resulting in instability and allowing for possible recurrence or worsening of the symptoms. The Maine and SPORT studies reported that surgical decompression outcomes were superior to those of nonsurgical measures. Randomization bias was the most significant flaw in both studies. It was clear in the 10-year outcome of the Maine study, that the benefit of decompressive surgery diminished over time and there was no significant differences

in lower back pain and patient satisfaction. Furthermore, those who underwent subsequent surgical procedures had less improvement in outcomes over time compared with patients who did not (18, 19).

A landmark study regarding the complications of open surgical treatment that the complication rate was 7% in spite of the highly skilled surgeons involved and the chance of death was one in one thousand. The rate of dural tear or spinal fluid leak in the surgical series was ranging from 2.0% to 20.0% in open surgery, and 1.1% to 12.5% in minimally invasive surgery. Castro-Menendez et al reported that despite those endoscopic surgeries were less invasive than open surgeries; they had an average procedure-related complication of 16%; with the most frequent being; incidental dural tear at a rate of 10% (16). Such complications usually require longer hospital stay, and possible additional surgery; all adding to health-care cost. Other serious complications like epidural hematoma and required blood transfusion were also reported after open and minimally invasive decompression surgeries.

Minimally Invasive Lumbar Decompression (*mild*) procedure:

The *mild* procedure, also commonly known as micro-decompression procedure, as the name implies is a mildly invasive, outpatient procedure typically performed in less than an hour. Using an imagining machine, it decreases the compression on the nerves by removing small bone tissues or hypertrophic ligamentum flavum by thinning, partially detaching, and remodeling the ligament (34).

Since the mild procedure requires no general anesthesia, no implants and no surgical incision thus no stitches; the complications associated with the *mild* procedure is definitely lower than the complication rates reported for both open and minimally invasive lumbar spinal stenosis surgeries. Patients are able to walk out same day and resume their regular activities with considerably less pain. The safety of the *mild* procedure and its permanent results has clearly been illustrated in several studies (35, 36).

Studies have also demonstrated that *mild* procedure is effective in relieving pain, decreasing disability and improving the walking distance and standing time in patients with moderate to severe lumbar spinal stenosis leading to an improved quality of life for patients. Also, a recent study from The Cleveland Clinic showed that *mild* procedure is the cost effective strategy as far as quality adjusted life year (QALY) is concerned in patients with LSS. To date, no study has found any additional potential harm exceeding the normal risks associated with any invasive procedure, making it a promising treatment for lumbar spinal stenosis in eligible cases.

THE POSTERIOR COMPARTMENT

Lumbar Facets (Zygapophysial) Joints Pain

According to the Association for the Study of Pain, pain originating from the lumbar facets joints make up 15-45% of all chronic low back pain. The common mechanism is inflammation of those joints due to repetitive stress and accumulating low-level trauma. The joint capsule is filled and stretched out with inflammatory fluid, thus generating pain. Predisposing factors include spondylolisthesis, degenerative disc disease, overweight and advanced age.

Diagnosis

Patients usually present with chronic low back pain that may be unilateral or bilateral, but does not usually lie right in the middle of the spine. It may be associated with referred pain. Pain from the upper lumbar facets might be referred to the flank, hip and upper lateral thigh whereas lower lumbar facets mediated pain is more likely to be referred to the thigh along the posterior and lateral aspect.

However, such referred pain is always above the knees and do not follow a specific nerve root distribution as in lumbar radiculopathy.

Although there are no characteristics findings in the physical examination, however, it is widely accepted that lumbar paravertebral tenderness may indicate facetogenic pain. Pain is usually reproduced with facet loading such as standing and/or extension and rotation maneuvers. Pain usually decreases with bending forward (flexing).

The lack of correlation between history and physical examination and the facet mediated pain resulted in the prevalent acceptance of the diagnostic blocks as a useful tool to establish the diagnosis. Recent studies deemed medial branch block (MBB) to be more beneficial than the intra-articular (IA) injections as a diagnostic tool. In addition, a positive result, identified as pain relief over a certain desirable percentage depending on the case, will help predict the prognosis of disease and whether it is recommended to proceed with a more permanent option like radiofrequency ablation (RFA) (37).

Several studies have showed a false-positive rate for lumbar facet blocks, ranging from 25% to 40% using comparative blocks or saline controls. This was regardless of the technique used whether IA or MBB. The reasons for false-positive facet blocks are multifactorial and include placebo response (18–32%), use of sedation, the copious use of superficial local anesthesia, and the spread of injectate to other pain generators.

On the other hand false negative results occur in 11% of the time. This was probably because local anesthetic never fully immersed the targeted nerves, or may due to aberrant or additional innervations to facet joints aside from medial branches.

For these reasons, it has been recommended to do double blocks, using either saline controls or two different local anesthetics, before proceeding to definitive therapy.

Treatment

Facet Joints Blocks

The use of intraarticular steroid injections to treat facet joint pain is controversial. In uncontrolled studies the response varied from intermediate pain to long-term relief. Long-term relief ranged from 18% to 63%. Most of the patients involved in those studies did not undergo diagnostic facet joint blocks. Intermediate pain relief has been reported after intraarticular local anesthetic alone.

No significant difference in outcomes between local anesthetic, steroid or saline injections. Another randomized, controlled study demonstrated a statistically significant benefit that favors steroid over saline at 6 months after the procedure. Based on the existing evidence 128,181,212–214, and the presence of inflammatory mediators in and around degenerated facet joints, a small subset of patients with lumbar facet joint pain may benefit from intraarticular steroid injections if accompanied by an active inflammatory process.

Radiofrequency Ablation:

Several uncontrolled trials have shown that radiofrequency denervation of lumbar facet joint pain, may provide sustained relief in 50–80% of subjects without previous back surgery and 35–50% of patients with failed back surgery syndrome.

Seven placebo-controlled studies have been conducted to evaluate the role of radiofrequency denervation in treatment of lumbar facet join pain. Six studies were positive and a non-interventional pain physician conducted the only negative study where patients' selection was not strict.

A large scale 10-year prospective clinical audit composed of 209 patients, also concluded that lumbar RFA was indeed a beneficial procedure in relieving pain. The audit found that 119 patients (68.4%)

had good (> 50%) to excellent (> 80%) pain relief lasting from 6 to 24 months (38). Another more recent systematic review also found similar findings supporting the relief of pain by undergoing lumbar RFA (39).

Complications:

Patient may complain of temporary paresthesia in the legs and temporary loss of motor functions, if large volume of local anesthetic was injected and spread to the segmental nerves.

Transient localized burning pain is one of the most common complications. The incidence of worsening back pain was 2.5 %, however, it was self-limiting lasting up to 2 weeks. Although they are uncommon but serious sequelae may follow facet joints steroids injections may cause suppression of the hypothalamic–pituitary–adrenal axis for a duration lasting up to 4 weeks, and impaired insulin sensitivity thus increasing the glucose levels for less than a week. Septic arthritis, epidural abscess, and meningitis; have been reported after intraarticular injections.

As for RF, transient and self-limiting numbness and/or dysesthesia have been reported after radiofrequency denervation. Although rare, burns may occur with RF due to electrical faults, insulation breaks in the electrodes, and generator malfunction. The most prevalent complication after RF is neuritis, with incidence less than 5%. The administration of corticosteroid was found to decrease the incidence of post procedure pain after radiofrequency denervation. There is also a potential risk of thermal injury to the ventral rami if an electrode is advanced ventrally over the transverse process.

Sacroiliac Joint Pain

Sacroiliac joint (SIJ) pain is a common cause of low back pain. The current literature estimates that in 10-30% of patients presenting with low back pain, the SIJ has been found to be the pain generator. Several risk factors leading to SIJ pain are identified. Pregnancy induced ligamentous laxity, trauma from motor vehicle accidents, athletic events requiring unilateral loading (cross-country skiing, in-line skating) and the spondyloarthropathies have all been implicated as underlying causes of SIJ mediated pain. Tumor, infection and occult fractures are other less common sources of SIJ dysfunction. Additionally, patients will often develop SIJ mediated pain following lumbar fusion surgeries as the biomechanics of the lumbar spine and the stresses transmitted to the SIJ are altered. The prevalence of SIJ dysfunction following lumbar fusion to ranges from 32-61%.

Despite numerous studies there remains no consensus regarding the innervation of the SI joint. The anterior SI joint has been found to have direct input ranging from the ventral Rami of L2-S2, whereas the posterior SIJ innervation travels through the dorsal Rami of L4-S3.

Diagnosis

The diagnosis of SIJ dysfunction or SI mediated pain is challenging at times since imaging are usually normal and other etiologies can cause similar low back pain. Initially SIJ dysfunctions are suspected based on the combination of history and physical examination. Skin over the SIJ may be tender to touch. Additionally, several tests might aid the diagnosis, one of which is FABER test, which induces pressure on the joint by having the patient lie down, flex the hip, abduct the leg, and externally rotate the hip which will induce pain (40).

Several studies have been conducted to determine the pain referral pattern most associated with SIJ mediated pain. Fortin et al injected asymptomatic volunteers with contrast and lidocaine in order to determine a pain referral pattern upon distension of the SIJ. SIJ mediated pain correlates to an area in the buttocks and radiating to the posterolateral thigh. There are single provocative or alignment tests that have been proven to accurately determine the SIJ as the primary pain generator in patients presenting with low back pain. However, there has been research suggesting that a combination of 3

positive provocative tests has led to a specificity of 78-79% and sensitivity of 85-94%. To add to the diagnostic dilemma there are very few radiographic signs to suggest SIJ involvement.

Treatment

The treatment of SIJ dysfunction usually includes conservative treatment with a multidisciplinary approach including medication management and physical therapy. Interventional procedures such as SIJ injections is recommended if conservative treatment fails and there is a need to maximize participation and benefits from physical therapy.

If the diagnosis of SIJ pain is confirmed with a diagnostic injection with local anesthetic alone the injection may be repeated with local anesthetic and corticosteroids to improve the duration of pain relief. If there is greater than 50% improvement in pain with transient results then the current literature supports the use of radiofrequency ablation. Conventional radiofrequency ablation (RFA) has been commonly used in the past with acceptable result but recent literature suggests that cooled radiofrequency ablation may produce improved results due to the larger lesions. When performing radiofrequency ablation of the SIJ innervation, it is common to create a strip lesion at the dorsal rami of L5 and the lateral branches of S1-S2 or 3 whose anatomic course can be quite variable. The theoretical advantage of cooled RFA is that a larger lesion can be reliably created to cover the variable path of the lateral branches of S1-3. Randomized placebo-controlled study using Cooled RFA on L5 primary dorsal Rami and S1-3 Lateral branches on 14 patients showed significant improvement at 1, 3 and 6 months follow up. Additionally, 11 of the patients in the placebo group were allowed to crossover and undergo conventional RFA. Again significant relief was shown in the crossover group.

If patients fail conservative and interventional treatment, surgical intervention may be the patient's last option for a meaningful recovery. A recent prospective study showed promising results in those who failed all other modalities.

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ANESTHESIOLOGY 2017
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Neurologic Disease and Non-Neurologic Surgery

Jeffrey J. Pasternak, MS, MD **Rochester, MN**

Patient co-morbidities often complicate anesthetic management. Neurologic diseases can impact systemic physiology. Likewise, aberrations in systemic physiology can adversely impact the injured nervous system. This refresher course will focus on common neurologic diseases and review their pathophysiology and major perioperative implications.

Learning Objectives:

1) Explain the pathophysiology of some common neurologic diseases
2) Describe the impact of these diseases on perioperative care
3) Formulate an appropriate management plan for patients with common neurologic diseases requiring anesthesia for non-neurologic surgery.

Stroke

Stroke is the onset of new neurologic deficits as a result of ischemia within the brain (88% of strokes) or hemorrhage within the brain or cranial vault (12% of strokes). In 2012, stroke was the second leading cause of death worldwide after heart disease and a major source of morbidity and consumption of health care resources by survivors of stroke.[1] Stroke related mortality is decreasing in the United States in recent years due to better control of contributing co-morbidities (ie, hypertension, hyperlipidemia, diabetes mellitus), smoking cessation, and greater awareness of stroke and risk factors for stroke. This session will focus on ischemic stroke.

The risk factors for ischemic stroke include (but are not limited to): increased age, male sex, African-American race, hypertension, hyperlipidemia, diabetes mellitus, smoking, personal or family history of stroke, obesity, and inactivity. A stroke should be strongly suspected in a person who develops focal neurologic deficits over the course of minutes to hours. Persons who have sustained a transient ischemic attack, ie, stroke symptoms that complete resolve within 24 h, should be considered at very high risk for developing a stroke. The signs and symptoms of stroke depend on the regions of brain affected by ischemia.

The risk of ischemic stroke in the perioperative period depends on the surgical procedure, with cardiac, major vascular, and neurosurgical procedures carrying the greatest risk. Exclusive of this high risk population, the overall risk of perioperative stroke in the general surgical population is about 0.1%, with patients having amputations at highest risk (0.8 – 1.1% depending on age).[2] Consistent risk factors for perioperative stroke include advanced age, renal failure, and a prior history of stroke.[2,3] Perioperative stroke is associated with an 8-fold increase in mortality at 30 d following surgery.[2]

Recent data confirm that institution of high dose beta-blocker drugs, especially metoprolol, in the perioperative period may increase the risk for stroke. [4-6] Therefore, beta-blocker drugs should be started with caution and titrated to effect in pharmacologically naïve patients.

In most circumstances, general anesthesia and regional anesthesia result in similar perioperative stroke risk.[2,7] However, in orthopedic patients having total joint arthroplasty, regional anesthesia may be associated with a lower risk of perioperative stroke.[8,9] Overall, intraoperative hypotension, anemia, hypoglycemia, and hyperglycemia should be avoided. In patients with pre-operative neurologic deficits, succinylcholine should be used with caution due to risk for hyperkalemia. Further, assessment of neuromuscular block with train-of-four stimulation should be avoided on weak extremities due to altered resistance to muscle relaxation with upper motor neuron injury.

Perioperative strokes may present as delayed emergence from anesthesia, inappropriate alterations in consciousness, or new neurologic deficits. In those with suspected stroke, brain oxygenation and perfusion should be optimized and a non-contrast computerized tomogram of the head should be obtained, along with an emergent neurology consult.

Spinal Cord Injury

Each year, there are an estimated 12,500-17,000 new cases of acute spinal cord injury in the United States and about 276,000 Americans living with chronic spinal cord injury.[10,11] Both acute and chronic spinal cord injury can have diffuse physiologic manifestations that can impact peri-procedural anesthetic management.

Acute Spinal Cord Injury

Anesthesiologists may be responsible for the care of patients with suspected or definitive acute spinal cord injury for non-neurosurgical procedures such as radiologic studies or for procedures related to other injuries. Spinal cord injuries are classified grossly as incomplete or complete injuries depending on where or not there is some degree of sensory or motor function below the level of injury. Most patients with acute injury enter a phase of spinal shock immediately following the injury that typically can last for 1-3 weeks. This consists of flaccid paralysis and can be accompanied by loss of sympathetic function below the level of injury. This latter phenomenon can lead to vasomotor paralysis and hypotension. For lesions in the cervical cord, loss of cardiac accelerator nerve function (usually derived from T_{1-4}) can lead to unopposed parasympathetic activity and bradycardia, exacerbating systemic hypotension. Hypotension in this setting can be detrimental as it serves to decrease perfusion to the injured spinal cord.

The respiratory system can also be affected in acute cord injury. For high thoracic or low cervical cord injuries, loss of intercostal muscle function can make ventilation dependent on phrenic nerve activation of the diaphragm. For high cervical cord injuries, loss of phrenic nerve function, derived from C3-5, can result in significant impairment or loss of ventilatory function.

Key points relevant to the care of patients with suspected or known acute spinal cord injury include:

a. Cervical spinal cord injury should be suspected in any patient who sustained major trauma, especially those with head trauma, ie, any force sufficient to injure the head can potentially injure the neck and vice versa.
b. Plain radiographs or computerized tomography of the cervical spine are not sensitive for detecting ligamentous injury. Thus, due to ligamentous instability, patients may be at risk for sustaining a cervical cord injury upon neck movement despite unremarkable plain radiographs or computerized tomographic scans.
    a. Efforts should be made to minimize neck movement during laryngoscopy and positioning for procedures.
    b. Hard cervical collars minimize but do not completely limit neck motion.
c. Hypotension should be treated to maintain perfusion to the injured cord.
d. Nitrous oxide should be used with caution if there is concern for breach of anatomic spaces such as pneumothorax or pneumocephalus.
e. Succinylcholine should be used with caution, especially > 24 h following injury due to risk for hyperkalemia.
f. Maintenance of normal body temperature may be challenging due to loss of sympathetic function and normal physiologic temperature regulation.
g. Avoid objects placed in the nose due to concerns for basilar skull fracture.

Chronic Spinal Cord Injury

Several weeks following spinal cord injury, cord reflexes return and patients enter a more chronic phase of their disease. The chronic state of spinal cord injury is characterized by:

a. A conversion from flaccid paralysis to spastic paralysis.
b. Increased risk for heightened autonomic reflexes (discussed later)
c. Impaired respiratory muscle function and the inability to effectively cough increases risk for hypoxemia, aspiration, and pneumonia in those with cervical or upper thoracic cord injuries
d. Incomplete bladder emptying that can lead to renal calculi and increase risk for infections that, in turn, can predispose to renal dysfunction
e. Pressure ulcers, muscle contractures, and increased risk for deep venous thrombosis
f. Depression and chronic pain

In addition to these considerations, the anesthesiologist should be aware that there is continued increased risk for hyperkalemia following the use of succinylcholine. Therefore, non-depolarizing neuromuscular blocking drugs should be considered if muscle relaxation is required. Further, monitoring muscle relaxation via train-of-four stimulation in weak limbs can lead to a false appearance of resistance to neuromuscular blockade. Drugs used to treat spasticity (ie, baclofen, benzodiazepines) should be continued in the perioperative period due to the risk of withdrawal.

Enhanced autonomic reflexes can be a major source of morbidity and mortality in patients with chronic spinal cord injury. The risk for autonomic hyperreflexia increases with higher levels of spinal cord injury. Specifically, patients with a spinal cord injury level at of higher than T6 are at highest risk whereas the risk is very low in those with injuries below T10.[12]

Somatic or visceral stimuli, such as pain or distention of the blader or rectum, initiate increased afferent activity into the spinal cord. In patients with an intact spinal cord, this activity is modulated by higher centers. In those with spinal cord injury, these stimuli lead to enhanced autonomic efferent activity below the level of the spinal cord injury resulting in significant vasoconstriction. As a result, systemic hypertension develops along with reflex bradycardia. In response to systemic hypertension, vasodilation occurs in regions innervated by cord segments above the level of the spinal cord injury. Patients may complain of headache, nasal congestion, and blurred vision. If severe, the patient may develop heart failure, pulmonary edema, or intracranial or retinal hemorrhages.

Management of autonomic hyperreflexia should focus on prevention. Painful procedures should not be performed on insensate regions of the body without anesthesia, to best ensure avoidance of autonomic hyperreflexia. General, neuraxial, or regional anesthesia are all possibilities, depending on the general health of the patient and the planned surgical intervention. For example, topical local anesthesia within the urethra is not adequate during cystoscopic procedures because bladder muscle proprioceptors may be stimulated during bladder distention. During labor and delivery, there is a theoretical advantage of spinal anesthesia over epidural anesthesia as sacral sparing with epidural anesthesia may increase the risk for autonomic hyperreflexia during delivery.

The anesthesiologist should be prepared to treat episodes of autonomic hyperreflexia. In patients receiving general anesthesia, deepening the anesthesia state may reduce to severity of the episode. For persistent hypertension, the patient should be treated with vasodilators such as sodium nitroprusside or hydralazine. Episodes of autonomic hyperreflexia may manifest after the procedure when anesthetic drug effects begin to wane. [13]

Multiple Sclerosis

Multiple sclerosis is the most common autoimmune disorder affecting the central nervous system, however the exact etiology of the disease is still unclear.[14] Approximately 2-2.5 million people are affected by multiple sclerosis worldwide, with women being affected twice as commonly as men. There appears to be a genetic predisposition and an increased incidence among persons living farther from the equator. Other associations include infections, stress, and smoking.[15-17]

Multiple sclerosis most commonly presents in patients in the third and fourth decades of life and is characterized by multiple relapses of symptoms. Although there may be improvement of symptoms following relapses, complete resolution of symptoms is rare. The pathophysiology consists of the combination of inflammation, demyelination, and axonal injury in diffuse areas of the brain and spinal cord, but not within the peripheral nervous system. Given the diffuse nature of the disease, clinical signs and symptoms depend on the locations of demyelination.

Making the diagnosis of multiple sclerosis can be quite difficult. Currently, diagnosis is based on the McDonald Criteria, [18] that depend on clinical signs and symptoms, findings on magnetic resonance imaging scans of the brain and spinal cord, and biochemical findings in cerebrospinal fluid. The classic finding on imaging is the presence of multifocal white matter lesions indicating demyelination. Oligoclonal bands are often found in the cerebrospinal fluid, indicating the production of immunoglobulins in the central nervous system.

Currently, there is no curative treatment for multiple sclerosis and management is targeted on symptom control and attenuation of the rate of disease progression. Generally, corticosteroids are the mainstay of treatment for acute relapses due to their antiinflammatory and immunomodulatory effects as well as their positive effect on blood brain barrier integrity. Although corticosteroids attenuate acute symptoms, their effect on long-term function and prognosis is unclear. Other immunomodulatory treatments for multiple sclerosis include interferon-β, glatiramer acetate, mitoxantrone, and azathioprine.

Anesthetic management of patients with multiple sclerosis can be complex. Patients should be made aware that anesthesia and surgery can increase their risk for a relapse. This may be due to increased physiologic stress, activation of the inflammatory cascade, fever, or, infection.[19,20] Increased temperature can exacerbate neurologic deficits due to multiple sclerosis, possibly due to decreased nerve conduction velocity at higher core temperatures.

Many patients with multiple sclerosis require chronic corticosteroids. As such, these patients may require additional steroid supplementation in the perioperative period. Further, the use of chronic steroids can predispose to hyperglycemia, electrolyte abnormalities, fragile skin, and infection. Use of other immunomodulatory drugs can also increase risk for infection. The clinician should be aware of side effects of specific drugs used to treat multiple sclerosis.

In patients with multiple sclerosis having general anesthesia, there is no current evidence to suggest a benefit or detriment to the use of specific inhalational or injectable medications. However, the clinician should be aware of concerns about the use of muscle relaxants. In patients with multiple sclerosis and evidence of upper motor neuron injury, the use of succinylcholine can predispose to hyperkalemia.[21] Also, resistance to muscle relaxation with non-depolarizing drugs can occur in affected extremities.[22]

In patients with multiple sclerosis who may be a candidate for regional anesthesia, there is concern that spinal anesthesia may increase the risk for relapse of symptoms. This has been attributed to direct toxicity of local anesthetics on the spinal cord already injured by multiple sclerosis and is based on limited data. However, spinal anesthesia has been used safely in patients with multiple sclerosis.[23,24] There is also risk for exacerbation of multiple sclerosis by epidural anesthesia,[25] although epidural analgesia has also been used safely in patients with multiple sclerosis.[26]

Seizure Disorder

A seizure is an abnormal excessive synchronous electrical discharge of groups of neurons in the brain. Approximately 5-10% of the population will have at least 1 seizure in their lifetime.[27] Epilepsy, a predisposition to recurring seizures, occurs in 4-10 per 1000 people worldwide, and there is an increased prevalence among those living in developing countries and of lower socioeconomic status.[28] Seizures are more common in individuals in extremes of age: in the very young, seizures are often due to congenital, metabolic, or infectious causes, or a genetic predisposition, whereas in the very old, neoplastic and vascular disorders are often the cause of seizures.

Seizures are broadly classified based on 2 characteristics: 1) whether the seizure affects part (partial) or all of the brain (generalized) and 2) whether there was (complex) or was not (simple) a loss of consciousness associated with the seizure. This broad classification leads to 3 primary types of seizures:

1) Simple partial seizures – no loss of consciousness and there is clinical evidence for only part of the brain being affected by the seizure (eg, rhythmic motor activity in only 1 limb). These seizures can undergo secondary generalization to affect the entire brain.
2) Complex partial seizures – generally affect the temporal lobe. Often consist of automatisms (eg, lip smacking, tugging at clothes) with loss of consciousness.
3) Generalized seizures – affect the entire brain and are always associated with an alteration of consciousness. Examples of generalized seizures include:
    a. Tonic-clonic seizures
    b. Absence seizures
    c. Myoclonic seizures
    d. Drop attacks.

Seizures should be considered as a sign of an underlying abnormality. Various drugs can increase risk for seizures (ie, ketamine) and seizures can occur during withdrawal of various drugs (ie, alcohol, benzodiazepines). Systemic conditions such as severe hypertension, preeclampsia, hepatic encephalopathy, porphyria, and uremia can increase risk for seizures. Of note, a specific cause for seizures is often not identified in many patients.

The relationship between anesthetic drugs and seizures is complex and not always additive. Drugs commonly associated with seizures include ketamine, enflurane, and sevoflurane. However, drugs associated with seizures or spike-and-wake electroencephalographic activity can often interrupt seizures once they have started (ie, substituted ether anesthetics, ketamine). In contrast, drugs known to be highly suppressant of seizures (eg, thiopental, inhaled anesthetics) can rarely be associated with seizure activity during anesthesia induction and elsewhere. [29,30]

Conditions that can mimic seizures include tics, torticollis, myoclonus, syncope, extrapyramidal reactions, and pseudoseizures. Pseudoseizures, or psychogenic seizures, represent a psychiatric disorder. Factors that could suggest a pseudoseizure include:

a. Resistance to antiepileptic drugs or response to a placebo
b. Events occur only in the presence of an audience (and not during sleep)
c. The apparent seizure can be categorized as simple generalized (ie, based on clinical presentation, the seizure appears to be affecting the entire brain but there is no alteration of consciousness)
d. There is a normal respiratory pattern with apparent generalized seizures
e. The apparent seizure consists of asynchronous movements.

The first line treatment for seizures generally involved trying to identify (and treat) the primary cause. In addition, pharmacologic therapy may also be utilized. Some patients may require multiple drugs to control seizures.

Additionally, some patients may also be a candidate for surgery, especially if a focal region of brain thought to be the primary source of seizure generation can be identified. In patients with refractory epilepsy, other options include corpus callosotomy (to minimize seizure spread to the contralateral hemisphere) or vagal nerve stimulation.

Perioperative management of patients with epilepsy includes continuation of antiepileptic medications, awareness of side effects of specific antiepileptic medications, and avoidance or minimization of drugs that lower the seizure threshold, if possible. The clinician should inquire about seizure phenotypes and frequency pre-operatively so that post-operative risk for seizures can be estimated and surveillance for seizures can occur in the perioperative period. Chronic use of antiepileptic drugs, especially phenytoin and carbamazepine, can shorten the duration of action of non-depolarizing muscle relaxants.[31] In patients with a vagal nerve stimulator, the cautery grounding pad should be placed far away from the device. Also, a vagal nerve stimulator should be deactivated in patients requiring magnetic resonance imaging.

Management of perioperative seizure should include:

1. Maintenance of airway, breathing, and circulation
2. Cessation of the seizure: consider benzodiazepines or other hypnotic drugs
3. Identification of a cause if this is a new seizure
4. Prevention of further seizures: treat the cause (if possible) and consider antiepileptic drugs such as levetiracetam

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ANESTHESIOLOGY 2017
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Common Pediatric Anesthesia Emergencies: Safety and Best Practice

R. Blaine Easley, MD **Houston/Texas**

Introduction:

Recent reports reviewing the status of pediatric emergency care have emphasized the fact that the majority of pediatric patients around the world receive emergency anesthetic care by general anesthesiologists.(1,2) In many community hospitals and surgery centers, general anesthesiologist provide safe and effective care to children undergoing routine surgery. However, in these same settings, clinically well children can acutely decompensate from medical and surgical issues before, during and after an anesthetic. While a comprehensive review of this subject is beyond the scope of this lecture, commonly encountered pediatric emergencies will be discussed along with current literature and resources for management by the general anesthesiologist.

Common Pediatric Emergencies:

Infants and children often present after-hours to community hospital emergency rooms (ER). Often this makes the "on-call" anesthesiologist one of the most valuable resources for airway management and vascular access in the acutely decompensating child. Common medical conditions requiring emergent management are shock (from dehydration or hypovolemia) and respiratory insufficiency (from pulmonary or central nervous system issues). Common surgical conditions requiring emergent involvement of the anesthesiologist are: trauma (like a supracondylar fracture), airway foreign body, appendicitis, post-tonsillectomy bleeding, sub-dural hematoma and pyloric stenosis (see FIGURE 1). Many of the medical issues resulting in respiratory distress and hemodynamic instability require similar management to those issues experienced in operating room (OR) or post-anesthetic care unit (PACU) environments when caring for pediatric patients. Again making the anesthesiologist a valuable resource.

FIGURE1: Common Pediatric Medical and Surgical Emergencies

Medical	Surgical
Dehydration	Trauma
Respiratory Disease	Burns
CNS disease	Airway Foreign Body
Sepsis	Appendicitis
Cardiac	Incarcerated Hernia
Metabolic disorder	Intussception
Toxic ingestion	Pylroic Stenosis
	Testicular torsion

General Preoperative Preparation: Ideally an ER, OR or PACU environment will have pediatric specific equipment and supplies available (i.e. intravensous/intraosseus catheters, central lines, endotracheal tubes, laryngoscope blades, etc.) Since many children are previously healthy before the emergency, a history can focus on a few common themes: 1) prior personal or family history of complications associated with anesthesia (like malignant hyperthermia); 2) personal history of prior anesthetics (this may allude to other comorbid conditions); 3) any problems that require visiting a doctor on a regular basis (including asthma, allergies, congenital heart disease, or other conditions or congenital anomalies). While asking about preoperative fasting guidelines are important, the majority will require an efficient assessment and anesthetic plan; making a rapid sequence intubation technique (RSI) necessary. For the purposes of this discussion, RSI or modified RSI will be used for securing the airway in the majority of clinical scenarios.

Based on the report from the Agency for Healthcare Research and Quality in 2012 the most common surgical procedures performed on hospitalized children ages (0-17 years; excluding circumcision and cesarean section) were appendectomy (103/100,000 population); bone fracture repair (20/100,000 population), and tonsillectomy (20/100,000 population). Given the prevalence of these urgent/emergent procedures in the community, a practicing anesthesiologist will most likely experience an emergent pediatric anesthetic case or complication.(2) The discussion will focus on six of the most common pediatric surgical emergencies in community hospitals:

1) Trauma/Fractured Long Bone (Opened reduction/fixation): Trauma is the leading cause of death in children 1-17 yo and accounts for almost 40% of deaths during childhood in developing countries.(3) While there is evidence that outcomes after trauma in children are best at specialized pediatric trauma centers, acute injuries often necessitate care at the nearest hospital.(4) There is widespread acceptance that uniform approaches to the injured child such as emphasized by Pediatric Advanced Life Support (PALS) and Advanced Trauma Life Support (ATLS) can improve communication and teamwork during pediatric emergencies.(5) Maintenance of certification in these programs can help keep practitioners up to date on evolving changes in practice. Regardless, the approach to an injured child is very comparable to an adult. Important differences are: **a)** Blood pressure is unreliable with regards to intravascular status. Children may be normal or hypertensive regardless of the severity of injury and can maintain perfusion with peripheral constriction with up to 75% of circulating blood volume absent, with minimal signs of shock. If signs of shock are present, such as peripheral circulatory restriction, tachycardia and/or confusion, then fluid resuscitation may be required before proceeding with any additional therapies. If there is evidence of delayed capillary refill (> 3 seconds) this finding correlates with a higher likelihood of shock.(5) **b)** Obtaining vascular access is a priority and peripheral venous cannulation is preferable. Consider the saphenous vein at the ankle and/or the external jugular vein – potential access sites that are often overlooked. Placement of an intra-osseous catheter into the tibia is a very effective and reliable method of gaining vascular access and is advised before attempts at central venous cannulation. In blunt trauma, hypovolemia should be treated with a bolus of 20 ml/kg of isotonic fluid (i.e. normal saline or lactated ringers solution), followed by reassessment and further boluses as required. In penetrating trauma with bleeding, 10 ml/kg should be given as the initial bolus, followed by another 10 ml/kg with surgical consultation at time of the second bolus. As a rule, one should consider transitioning to blood product administration after giving 40-60 ml/kg of crystalloid (sooner if blood loss is evident). c) Respiratory distress may be multifactorial from shock, anxiety, pain and injuries. While rib fractures and flail chest are less common in children compared to adults; hemothorax and/or pneumothorax may be present with minimal clinical or external signs of injury. In addition, children will often swallow air when distress making their stomachs distended increasing their risk of vomiting and further reducing their functional residual capacity. This net reduction in functional residual capacity makes preoxygenation a crucial part of preparation for tracheal intubation. **d)** Management of the pediatric airway may pose challenges for those unfamiliar with children. Infants and babies have a larger head and higher, more anterior larynx compared with older children and adults. The higher metabolic rate in young children combined with the decreased functional residual capacity that is often seen in trauma patients will result in a rapid desaturation if airway management is not optimal. After circulation, airway, and breathing and have been stabilized, an assessment of disability should be made using the AVPU scale (Alert, responsive to Voice, responsive to Pain or Unresponsive). Formal Glasgow Coma Scale (GCS) assessment should take place as part of the secondary survey. During the primary survey, careful attention should be paid to keeping the injured child warm. The critical role of appropriate pain management has been recognized in pediatric trauma, and anesthesiologist caring for injured children must have good working knowledge of appropriate drugs and techniques.

Fortunately most traumatic injuries in children are not severe and are often isolated to an extremity fracture that requires urgent or emergent treatment. Supracondylar femur fractures represent 12% of femur fractures and very common in children 1-4 yo, while distal arm fractures make up 20-30% of fractures requiring surgery. Boys accounted for 61% of all fracture events, with a male:female ratio of 2:1 in childhood and 3:1 in adolescences. The peak incidence of fractures occurs at 11-14yo with a seasonal peak in Summer months.(6) Mechanism of injury include: trauma from automobile accidents, falls during play or sports and inflicted injuries. Most of these children are healthy and have sustained an injury while in a playground or at school. Of note, they may have significant pain and may require immediate surgery.

Preoperative preparation: While NPO time is important, it may be irrelevant as presence of the injury and pain medications may reduce gastric emptying resulting in a high-risk for a full-stomach. Studies have shown that nearly half of patients will have gastric aspirates greater than 40 ml/kg after 8 hours of NPO status following a traumatic fracture.(7)

Induction and Maintenance of Anesthesia: Timing of the procedure depends on the vascular and neurologic status of the limb. If no compromise, we still attempt to get these patients to the OR within 6 hours of presentation. While the anesthetic is straight forward, if <8 hours an RSI technique is used to secure the airway secondary to concerns of a "full stomach" while longer NPO times >8 hours may result in laryngeal mask airway placement; followed by a combined general and regional technique. A combined general and regional anesthetic technique offers the advantage of lower intraoperative general anesthetic requirements and the provision of postoperative analgesia, but its use must be discussed with the surgeon before placement.

For example, in the event of a fracture of the humerus, there is great risk of compartment syndrome and neurovascular compromise. Sensory testing postoperatively is essential but may be difficult or impossible if a nerve block has been placed. In contrast, regional anesthesia may be of great importance to the recovery after procedures in which the extremity will benefit from the vasodilatory properties of the sympathectomy caused by the local anesthetic, or in an amputation in which preemptive analgesia may diminish phantom pain. Ultimately, the use of a regional technique is full discussed with the surgeon and deferred if they have concern.
Postoperative complications: If regional anesthesia would be of benefit, but the child is still at risk of compartment syndrome, compartmental pressures should be measured frequently by the surgical team. Compartment syndrome, even in the presence of a block, usually presents as breakthrough pain.(8) In all cases of regional block placement in children, particular attention must be paid to adherence to dosing guidelines to avoid the risks of local anesthetic toxicity. Conservative maximum allowable dosing is as follows: levobupivacaine of 2 to 2.5 mg/kg or ropivacaine of 3 mg/kg. Test dosing with epinephrine (5 mcg/ml) in the local anesthetic solution may help the practitioner recognize intravascular injection. While there is growing practice for doing regional techniques with emergent fracture surgery in pediatric and adult patients, if an anesthesiologist does not perform pediatric regional techniques often, then an emergent scenario should not be the time to attempt this approach. Typically post-operative opioids and acetaminophen are adequate for pain control.

2) Airway foreign body: Airway foreign body (AFB) is a major source of morbidity and mortality in children under 5 yo, with a peak incidence at 2 yo. Though it was originally thought that death from AFB was rate if the child reaches the hospital, recent studies suggest a hospital mortality rate of 3.4%.(9) Depending on the location of the aspirated object removal can often be life-saving. A careful history may recall a remote history of choking that appeared to resolve only to result in a later presentation with respiratory symptoms. There is usually a history of cough or persistent wheezing, hoarseness and asymmetric lung exam. Very rarely there is stridor or significant desaturation. Stable symptoms may suggest an immobile AFB; while a history of fluctuating symptoms such as intermittent stridor or wheezing may be an indicator of a mobile AFB, which can be life-threatening. Of all the presenting symptoms and signs, a choking episode has the highest sensitivity and specificity for an AFB. Organic
Preoperative evaluation: A plain film of the chest may be obtained by the emergency department doctor before consultation of the otolaryngology service. This could reveal a foreign body (if radio-opaque) or may demonstrate collapse of the lung or hyperinflation. Generally organic material like peanuts may not be seen in a plain film. Historic information including the ingestion of organic material can usually be obtained and could give a clue to the foreign body. Often these children are toddlers, they are fussy and can be very difficulty to console. Premedication is not usually warranted. We have taken parents to the OR to prevent the child from getting upset at the time of induction of anesthesia.
Induction and maintenance of anesthesia: There are multiple methods reported in the literature regarding the anesthetic management of foreign body retrieval in children. The three techniques include inhaled induction with spontaneous ventilation; TIVA using propofol and remifentanil with spontaneous ventilation; and using controlled or manual jet ventilation. If possible, IV access is usually obtained in the ER. A smooth mask induction with spontaneous ventilation with sevoflurane and oxygen is then performed. After securing the airway, the most common approach is to allow for spontaneous ventilation since there is a potential for dislodging the foreign body during retrieval. Factors associated with hypoxemia include younger patient, plant seed (organic) AFB, long surgical duration, pneumonia and in some instances spontaneous ventilation.(10) A variety of ventilatory modes, especially jet ventilation may have potentially benefit children but must be coordinated and prepared for with the surgeon – since control of the airway during the procedure will be shared. While TIVA has been associated with longer breath holding there is the association with adverse issues of longer duration of emergence and potential for laryngospasm. Ultimately, maintenance can be achieved using either inhaled anesthetics or IV infusions.
Foreign Body removal: The AFB can be removed using several techniques. The common technique is to use a rigid ventilating bronchoscope with a forceps to retrieve the foreign body. This technique has been shown to be 95-98% successful. More recently, fiberoptic bronchoscopes have been used to retrieve the foreign body. The main problem is when the foreign body is lost while in the process of retrieval especially if lodged in the main trachea. The most important and potentially life-saving technique would be to advance the foreign body to one of the bronchi and ventilate the child through the other lung. Children tend to desaturate rather rapidly and the situation could become dangerous. It is important to prevent coughing and bucking, some anesthesiologists and/or surgeons use 1% lidocaine spray for the cords before airway instrumentation.

Postoperative complications: These include creation of smaller AFB in distal airways, pneumonia, laryngeal edema, bronchospasm, hypoxic cardiac arrest, pneumothorax, pneumo-mediastinum, tracheal and bronchial laceration. It is imperative that there is communication with the surgeon before and during the procedure. Since these patients are at risk for sub-glottic edema treatment with dexamethasone (0.5-1.5 mg/kg) begins in the OR with continued treatment may be desired by the surgeon for up to 3 days. If symptoms of stridor or issues of desaturation, prolonged periods of PACU observation and/or admission for continued monitoring may be warranted. The outcome of the child is based on proper communication as well as the superb skills of the surgeon and the anesthesiologist.

3) Acute Abdomen/Appendectomy: Acute appendicitis is the most common surgical condition of the abdomen, with a 7% lifetime risk. While complications and death from appendicitis is rate (<1%) the rate of perforation in young children (<4 yo) is 80-100% compared to 10-20% in older children and adults. Perforation is associated with higher morbidity and mortality. The differences in perforation rates are most likely related to the lack of focal symptoms in younger children. Symptoms in younger children are often irritability, nausea, vomiting and diffuse abdominal pain. False appendectomy rates are between 5-25% in younger children and current diagnostic and management practice are utilizing additional imaging modalities (like CT and MRI) to better assess likelihood of the appendicitis and perforation.
Preoperative preparation: This has resulted in earlier courses of antibiotics and re-hydration therapy with a period of observation if the possibility of rupture seems low. This creates a scenario of an urgent procedure in a more stable patient, rather than an emergent procedure in an unstable patient.
Induction and maintenance of anesthesia: Usually anesthesia for appendectomy is straight forward utilizing a RSI and general anesthesia. Laparoscopic approaches are more prevalent, though classic open incisions are performed at the discretion and experience of the surgeon. Recent studies have demonstrated transversus abdominal plane (TAP) blocks to reduce acute opioid needs, but may not alter overall need opioid requirements.(11)
Postoperative care: If no perforation or rupture and a laparoscopic procedure, patients are typically extubated, undergo routine recovery and have pain management with ketorolac, acetaminophen and oral opioids. The addition of patient controlled analgesia is usually required in those undergoing open procedures or with perforation and peritonitis. Of note, patients with perforated appendix typically require a more involved perioperative fluid resuscitation that extends into the post-operative period.

4) Acute Abdomen/Pyloric Stenosis: This is a fairly common emergency that can occur at most institutions. There is an incidence of 1:500 in all live births with a propensity to occur in firstborn males. They are often healthy infants who otherwise have a recurrent history of vomiting and often present to the emergency department with significant dehydration. They often present with hypochloremic, hypokalemic metabolic alkalosis. However, there are studies that also observed a hyperkalemic state in some infants.
Preoperative preparation: It is crucial that the infant is well hydrated. These infants are generally significantly dehydrated with absent skin turgor and with a sunken fontanel. In addition, due to significant vomiting, it is important to ensure that the child is also not hypoglycemic at the time of presentation. Adequate rehydration should occur prior to the induction of anesthesia, since the surgery should be thought of as, "urgent but never emergent."
Induction and maintenance of anesthesia: A RSI is generally planned with adequate pre-oxygenation since these infants have a tendency to desaturate rapidly. The use of a small dose of hypnotic followed by a muscle relaxant will allow for adequate placement of the endotracheal tube. Studies comparing succinylcholine versus a non-depolarizing drug like rocuronium have shown the time to recovery may be slightly prolonged with the non-depolarizing drug.(12) Like with the prior section on appendectomy, the surgical approach will dictate post-operative pain requirements. If a laparoscopic procedure, careful attention has to be paid to the insufflation pressures for the abdomen with can significantly reduce functional reserve capacity and venous return by collapsing the inferior vena cava in an infant. Comparison of an open sub-umbilical approach has been compared to a laparoscopic approach, with the laparoscopic technique being associated with a faster recovery and a shorter operating time.(12)
The maintenance anesthetic can be achieved with either inhaled anesthesia or a Total IV anesthetic (TIVA) anesthetic. Studies of TIVA versus inhaled anesthetics demonstrate a more rapid return to baseline with ultra-short-acting opioids like remifentanil.(12) Most recently the addition of a regional TAPS blocks for managing pain in the postoperative period has demonstrated the acute reduction and potential elimination of opioid need for the surgery, with potential benefits of further reducing post-operative apnea risks and monitoring needs in this infant group.
Emergence and postoperative care: Again with a focus on reducing post-operative respiratory issues, emergence from surgery and extubation is typically performed in a fully awake patient. Maintaining an IV access is important

for the infant to ensure adequate hydration and glucose delivery in the immediate postoperative period. These children do very well and often have a rapid recovery to their normal state within hours of surgery.

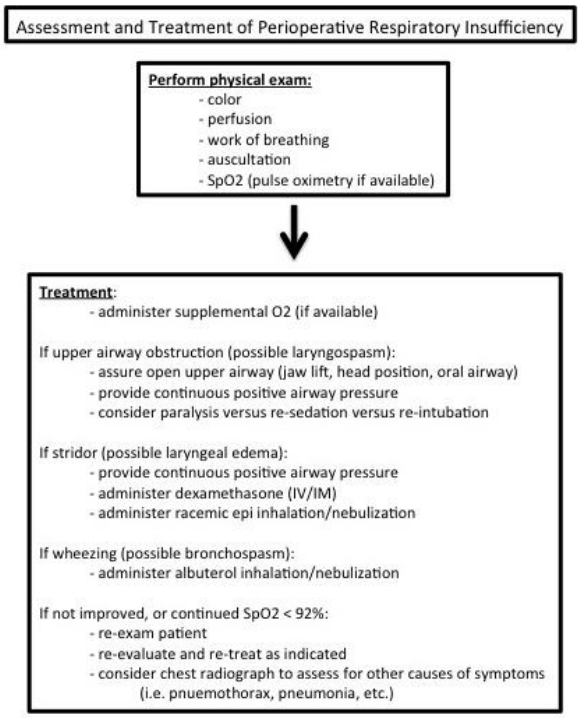
5) Post-tonsillectomy Bleeding: Tonsillectomy is one of the most common pediatric surgical procedures. Post-tonsillectomy bleeding is a serious complication. There are many factors that may lead to bleeding including poor hemostasis, bleeding diathesis (including von Willebrand disease), infection, and foreign body irritation. Tonsillar bleeding occurs in 2 phases, an early phase (within the first 24hours) that is associated with poor hemostasis or bleeding issues, and a secondary bleed that occurs in the first week (between postoperative days 4 and 7), which is associated with secondary infection. In the majority (66%) of children, bleeding occurs within the tonsillar bed, 27% in the nasopharynx and 7% from both locations. In a large retrospective study, the incidence of post-tonsillectomy bleeding was 2.15%. Therefore, the patient with bleeding tonsils may present as an inpatient or via the ER as an outpatient. Major post-tonsillectomy bleeding may be sudden resulting in high-risk patient with hypovolaemic shock and airway obstruction.(13) Rapid deterioration is possible, and the urgency to proceed to the OR must be balanced with appropriate access and stabilization of the patient if eminent respiratory and/or hemodynamic collapse can be avoided through aggressive volume and/or blood product resuscitation.
Preoperative preparation: Calculating the volume of blood loss may be difficult, as the child may have swallowed significant amounts. Intravenous access should be secured and intravenous fluid resuscitation commenced. Hemoglobin and blood cross-match should be sent along with coagulation profiles. Preparation for a potential difficult intubation with adequate airway equipment and immediate surgical availability is essential. Checking arterial blood pressures and pulse pressures may be useful to determine if they are compromised. In addition, looking for skin turgor as well as checking for orthostatic hypotension especially in the older child may point to an acute hypovolemic state. Blood should be sent for type and cross-match and if it is an emergency, and if the child looks quite hypovolemic, it may be necessary to have blood available in the OR before induction of anesthesia.
Intraoperative management: There is a paucity of published papers on the anesthetic management of post-tonsillectomy bleeding. Both intravenous and inhalational induction techniques have been described, with a RSI being the most common approach.(14) A retrospective study of post-tonsillectomy bleeding found a difficult re-intubation rate of 2.7%.
Induction of anesthesia: The child is likely to be anxious. Again, emphasis should be on the adequate hydration and availability of fluid and/or blood products to continue hemodynamic resuscitation. Since the child is likely to also have a full stomach as they potentially could have swallowed a large amount of blood from the oropharynx. Attempts to keep the child with its face turned to the side may be helpful in keeping blood from being aspirated. A RSI is usually planned with either propofol or ketamine (if the child is unstable) and succinylcholine or high dose rocuronium. Typically a stylet and smaller sized, cuffed endotracheal tube is utilized in anticipation of potential airway edema and clot. After securing the airway, the surgeon should be ready to look for active bleeders. In the event there is no active bleeder that is visualized, there should be further investigations including a follow-up coagulation profile including platelet count and hemoglobin. This may reveal a potential for an acquired or inherited disorder of coagulation. Given the nature of the procedure, antiemetic therapy with 2 or more agents is typically provided before extubation since these patients have a propensity to vomit after surgery.
Postoperative period: Given the dynamic and life-threatening nature of a routine outpatient procedure can change turning into a surgical emergency, it is important to observe the patient for at least 6 hours post-procedure with consideration for overnight observation.

Pedi-Crisis Checklist:
The application of perioperative checklists has greatly enhanced safety and efficacy of care in adult patients. Recently data has grown to demonstrate enhanced outcomes for pediatric-based checklists to improve perioperative handoffs, deep vein thrombosis-risk and reduced blood stream infections. Intraoperative checklists before initiation of surgery have resulted in reduction of wrong-side surgery and improved team work in the OR environment. Recent studies in adults have demonstrated checklists to improve crisis management – like intraoperative arrest.(15) To improve the quality and content of pediatric care, a pediatric crisis checklist has been developed to improve access to current clinical guidelines and assist in more effective pediatric emergency management in the OR by the anesthesiologist. While studies of the pediatric crisis checklist in simulation and clinical management are underway, the utilization of these checklists are growing and currently available via this link to the most up-to-date version.
http://www.pedsanesthesia.org/wp-content/uploads/2015/12/CriticalEventsChecklists_12142015.pdf

Common Post-Anesthetic Emergencies:

Perioperative breathing problems are common in children, and we recommend a standard way to examine airway and breathing, and ways to evaluate and treat a child with breathing problem. We listed the order or problems, from the most common intraoperative issues to most common post-anesthetic issues. Frequent examination of the patient to determine the cause of hypoxemia and respiratory distress is necessary and often may be dynamic, the anesthesiologist to make repeated evaluations of the patient in order to refine therapy. (see **Figure 2**).

FIGURE 2: Algorithm for management of perioperative respiratory insufficiency



Laryngospasm, the involuntary contraction of the glottic muscles (vocal cords) leading to tight closure of the glottis, happens quite often in pediatric anesthesia and can be a bad problem resulting in blockage of the airway, admission to the hospital, need for a long time in PACU, and sometimes intubation and mechanical ventilation. If laryngospasm is very bad, it can cause negative pressure pulmonary edema---fast onset of rales, respiratory distress, and hypoxia.(16) Laryngospasm can happen any time during or after an anesthetic, the risk of laryngospasm is highest immediately after tracheal extubation and may be increased by stimulation of the patient during emergence, such as suctioning the airway. Laryngospasm happens more often in younger patients. Laryngospasm can also happen in the OR or PACU, especially when the endotracheal tube was removed "deep" and who then emerge from anesthesia in the PACU. The first treatment is continuous positive airway pressure (CPAP) via facemask with 100% oxygen, which often is all that is needed. Some patients will require deepening of the anesthetic (like a bolus of propofol or other induction agent) in addition to CPAP. The treatment that almost always treats laryngospasm is neuromuscular blockade with a small dose of succinylcholine IV (0.1 mg/kg) or IM (0.3 mg/kg) to relax the vocal cords. When the laryngospasm breaks, the anesthesiologist can support breathing with bag and mask ventilation, or sometimes the patient's trachea needs to be intubated.

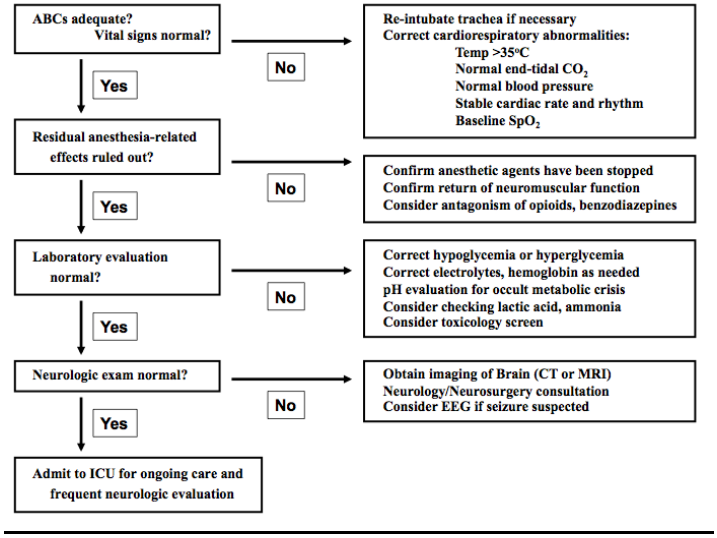
Post-extubation stridor is a changing inspiratory upper airway obstruction that can occur in any age group, but happens more often in pediatric patients due to anatomic differences of the airway. Because the subglottic region (below the vocal cords) is the narrowest portion of the pediatric airway, an endotracheal tube that has been inserted easily through the true vocal cords may still cause pressure resulting in edema and/or necrosis of the subglottic mucosa. Also because the pediatric airway is smaller than the adult, when there is mucosal edema, even if mild, then the airway obstruction can be severe. This is made worse a relative floppy upper airway and by increased negative intra-thoracic pressure; this leads to respiratory distress with inspiratory stridor. In its severe form, the anesthetist can hear expiratory sounds as well; in patients with little to no ventilation (moving almost no air), many

times there is no stridor. The first treatment is inhaled vasoconstrictor (e.g. nebulized racemic epinephrine) to decrease tissue edema. Giving racemic epinephrine (2.25%) 0.25mL in 3cc normal saline via high-flow nebulization, and repeating up to 3 times with humidified oxygen in between treatments, is the first treatment. Corticosteroids may also be administered for a longer-acting, anti-inflammatory effect. Those patients that receive multiple racemic treatments and/or corticosteroids are often admitted to the hospital for observation. Dexamethasone at a dose 0.5 mg/kg/dose IV every 6 hours for four to six doses (24-36 hours) often works well. Prophylactic steroid treatment in patients with a history of stridor, croup or subglottic narrowing may be helpful. Treatment of every small child should not be done. Rarely, patients may require re-intubation for significant obstruction. If re-intubation is needed, a smaller endotracheal tube than the one placed for surgery should be used, and dexamethasone treatment for 24 hours should be given. If stridor happens again, evaluation by an ear, nose, and throat surgeon by bronchoscopy may be needed to examine the glottis and trachea for other abnormalities (such as arytenoid dislocation or other trauma, tracheitis, or airway granuloma).

Bronchospasm, (wheezing) or reversible bronchiolar smooth muscle constriction leading to air-trapping, respiratory distress, and the clinical sign of expiratory wheezing, is the main sign of asthma exacerbations. Bronchospasm is most commonly seen in known asthmatics, but it can be seen in any patient after endotracheal intubation and/or extubation through direct irritation of the airway. The first treatment for wheezing is inhaled beta-agonist therapy (e.g. albuterol). However, anesthetic gases work very well to relax airway smooth muscle, and may be used (if blood pressure is not to low) to treat severe wheezing in the OR. If the wheezing is not severe, inhalational bronchodilators may be sufficient. The patient with moderate to severe bronchospasm may require more treatment, with administration of steroids (like methylprednisolone 0.5 to 1 mg/kg/dose IV every 6 hours, max dose 80 mg/day) and possibly subcutaneous epinephrine (10 micrograms/kg/dose subcutaneously, max dose 0.5 mg). If all these treatments do not work, continuous infusions of adrenergic agents (e.g. terbutaline, epinephrine) are often used and work most of the time.

Delayed Emergence and Emergence Failure- at the end of surgery, anesthetics are stopped and the patient emerges (wakes up) from anesthesia as described above. While most of the events that happen are respiratory in nature, sometimes even with a very good anesthetic, patients might not wake up quickly.(17) In this event, the anesthesiologist should follow an algorithm to decide on the potential causes and treatments (see **Figure 3**).

FIGURE 3: Algorithm for management of delayed emergence



First steps are to be sure oxygenation, ventilation, and circulation are all normal. Check the pupils next--,if they are of equal size, small to medium size, and react quickly to light, a serious brain problem is less likely. Assess a core temperature (rectal or oral) again to be sure there is not hypothermia or severe hyperthermia. Next, too large a drug dose, or leftover anesthetic effect should be checked. Look carefully at total doses of both intravenous drugs and anesthetic gases. Examination of pupils (see above) may help to decide if the patient received too much opioid like morphine or fentanyl. If the pupils are very small ("pinpoint") then they may have gotten a large dose. Reversal of muscle relaxation should be checked with a twitch monitor. If no improvement, begin a check for derangements of glucose, electrolyte, or other metabolic issue. A blood sample should be sent for glucose (exclude hypo or

hyperglycemia), arterial blood gas (hyper- or hypo-carbia), and electrolyte measurements (i.e. sodium, low potassium, low calcium, high magnesium). Once in a while, severe anemia that is not realized may be seen as coma, and so hemoglobin should be checked as well. The anesthesiologist should be aware that rare genetic diseases might cause in metabolic crisis with mental status change or weakness (like periodic hypokalemic paralysis). This might happen for the first time in the pediatric patient during a stressful event such as an anesthetic. If all of these tests do not give a cause for delay in awakening, the patient should have a more thorough neurologic assessment including a pediatric neurologist or neurosurgeon, if available. Independent of consultant availability, radiographic imaging to look for stroke (i.e. computed tomographic (CT) scan or magnetic resonance imaging (MRI)) followed by ICU admission or transfer to a tertiary care center with pediatric resources for ongoing evaluation and management.

Conclusions:
With proper preparation and resources the general anesthesiologist should be comfortable in managing common pediatric emergencies. Clinical resources are available and can be incorporated into routine and emergent care to make managing pediatric emergencies in the perioperative period safe and effective.

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ANESTHESIOLOGY 2017
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Leading Change in Anesthesiology and Perioperative Medicine

Berend Mets MB. ChB. Ph.D. F.R.C.A. **Hershey, Pennsylvania**

Objectives:

To Understand the Concept of Leadership in Relation to Change Management
To Recognize the Key Ingredients that are Part of Any Successful Change Initiative
To Illustrate how a Change Initiative can be Performed in Perioperative Medicine

Creating the Appropriate Environment
The role of Leadership is to create the appropriate environment which will allow clinicians to be successful in their individual and collective endeavors. As healthcare is becoming more a business than medical care, the role of the Anesthesiologist/Physician leader appears diminished (1) when it should in fact be enhanced. The goal of this lecture and summary is to empower the Anesthesiologist with the necessary leadership and change management principles to effectively lead a change initiative.

Ensuring Optimal Team Functioning
As perioperative care becomes ever more complex a leadership challenge is to develop interdisciplinary teamwork recognizing teams as "a small group of people with complementary skills who are committed to a common purpose, performance goals and approach, for which they hold themselves mutually accountable" (2).

Dealing with Change
The only constant in todays periop environment is change. To continue to be successful, individuals and anesthesiology groups need to be able to change as individuals, and collectively as a perioperative care team. This is because the external landscape is continually changing (3).

In the following text we will outline the concepts of Leadership and Management from contemporary business literature, and then describe a "framework" within which leadership can occur (4,5).
We will conclude with how Leadership and Management principles can be applied to the Perioperative Setting.

Definitions of Leadership

- "Leadership is the accomplishment of a goal through the direction of human assistants." (6)
- "The first responsibility of a leader is to define reality. The last is to say thank-you. In between the two, the leader must become a servant and debtor." (7)
- Leadership has also be defined as the electricity that runs through an organization.
- "Leadership defines what the future should look like, aligns people with that vision, and inspires them to make it happen despite the obstacles." (8)

Relationship of Leadership and Management
Leadership and management are interdependent and both essential to effective functioning. They are complimentary but not the same. "Managers do things right and leaders do the right thing"(9) is oft quoted. In fact managers create order, predictability and stability through planning and budgeting, organizing, staffing, controlling and problem solving. Instead leadership is about coping with and producing constructive change (11), in this process, Leaders are "chief disorganizers" through probing, challenging and finding better ways of doing things (12).

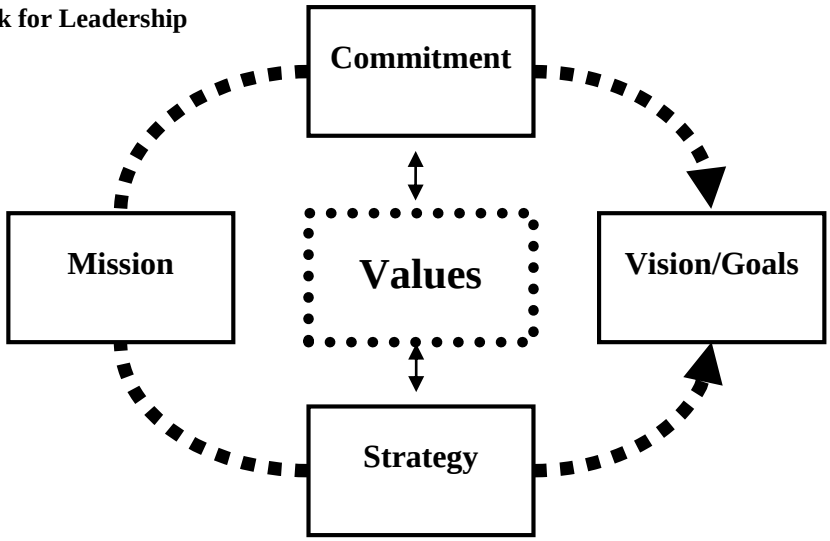
Attributes of Successful Leaders
Kouzes and Posner have identified the key characteristics that followers seek in their leader (13). In the course of their work, these investigators surveyed more than 75,000 people in 6 continents over a period of more than eleven years and asked; "what do you expect from a leader that you would willingly follow?" The four characteristics most

consistently identified by the highest percentage of respondents, were, that they wanted their leaders to be: Honest (88%), forward looking (71%), competent (66%), and inspiring (65%) (13).
Effective leadership is dramatically ordinary stuff according to a George Binney, a management consultant (14). The three leadership qualities that are most important in business are (i) A clear sense of direction and the ability to communicate this, (ii) A knack for motivating people, and (iii) a measure of adaptability (14).
Referring to our own specialty, in a survey of Chairpersons of Academic Anesthesia departments, we found that fully 64% had decided, as a career goal, that they wanted to take on the leadership of a department early in their career (when they were a fellow or Assistant Professor). Further, 30% had been Chairs previously and 29% had been previous Vice Chairs while 28% had been Division Directors. This suggests future academic leaders planned their career experience to prepare to lead Anesthesiology departments (15).

Emotional Intelligence (role modeling)

Some would say that the key leadership competency is that of emotional intelligence. This is because, the Leader's "emotional style" or mood is quite literally contagious (16). This sets the tone for the work environment and culture. Thus the leadership challenge is for leaders to regularly be optimistic, and energized so that through their chosen actions colleagues feel and act in the same way (16). More specifically, Goleman has defined leadership with respect to 6 leadership styles, namely, *visionary*, *coaching*, *affiliative*, *democratic*, *pacesetting* and *commanding*. Leaders use these styles to varying degrees at different times. In a survey of Anesthesiology Chairs in the USA, Chairpersons ranked Visionary and Coaching styles as most commonly used, while a Commanding style received the lowest rank order (34).

Framework for Leadership



A simple way to view the framework within which leadership occurs (17), is according to the adapted schema depicted above.

Our ***Mission*** in anesthesia may include clinical care, quality, education, research and possibly community outreach.

Shared Values (such as *respect*, *integrity*, *collegiality*, *compassion*, as well as *excellence* are the enduring beliefs that drive decisions and strategy in a department (8).

A key goal is developing a ***Vision*** for the endeavor based on established values (8). A vision is not something "mystical" but a practical embodiment of a goal, which is both inspiring and sets direction.

Strategy are the actions that will be taken to achieve the established vision and goals (21). An example of strategy in an academic department, defines not only what will be done, but more importantly determines what will not be done.

So a department that has the Vision of being number one in National Institutes of Health (NIH) funding would not invest in research endeavors unlikely to result in NIH grant applications.

Commitment by an individual is the energy and creativity that people bring to the department to ensure success (20). Leaders cannot command commitment only inspire it. It is built through identifying an individual's passion and through the sharing of accountability and responsibility (13).

Teaming

The hallmark of a team effort is both individual and mutual accountability and a common commitment to a goal (2). A study of 16 cardiac surgery teams who together developed a new approach to cardiac surgery, the Heartport system, and comprising teams of surgeons, anesthesiologists, nurses and perfusionists has highlighted commonalities in successful teaming (24). This procedure which is complicated and involves, TEE monitored endovascular clamping, and minimal surgical incision size, required more interdependence and communication between clinicians than conventional cardiac surgery. An important lesson was that the most successful teams, (measured as the average improvement in procedure duration times) had team leaders who actively managed their teams learning efforts.
While the procedure initially took 3-4 times longer than usual; the pace of improvement differed dramatically from team to team. The authors (24) identified factors that improved team success. Important factors were found to be the selection of a consistent team of members based on competence, willingness to work with others and the willingness to accept ambiguous situations and converse with members of higher status. In addition, framing the challenge as organizational (rather than technical, vide infra) was also important. Finally, creating an environment of psychological safety and allowing "learning in action" sped team performance.

Change management

Change is difficult (8). This is so because often what we did in the past works, is comfortable and the need to alter is not clearly apparent. This leads to the quote so often heard as a counter to the wrenching process of change: "If it ain't broke don't fix it". The Center for Creative Leadership has conducted an inventory of the 10 flaws that can result in managerial derailment. The most commonly cited reason for derailment was the inability to adapt (change) and the most common cited success factor in North America was the ability to develop or adapt (26).

Understanding Technical vs. Adaptive Change

At its essence, it is important to define the Challenge of the required change as a *technical* or an *adaptive* challenge. To understand this concept better, think of an individual who has just been diagnosed with coronary artery disease (CAD).
A technical solution to this problem would be to schedule him/her for a CABG operation. However an adaptive challenge would be asking the individual to change their behavior to improve the potential outcome from CAD, through a change in eating and smoking habits and through starting an exercise program to compensate for a previous sedentary life style.

Leadership Role

In such change initiatives the leadership role is complex. It is crucial that the leader is able to understand the problems on the ground i.e. the "dance floor" while also being constantly able to remove themselves from the action on to the "balcony" to see the big picture (27). The leader needs to regulate the inevitable distress that occurs keeping enough pressure so that people feel the need to change while avoiding colleagues from becoming overwhelmed (28). To achieve this the leader needs to attend to three areas (28). Firstly a "holding environment" must be established where the issues, norms and values needed are debated and shaped and from which these are communicated to the organization. The leader needs to establish priorities and focus, (not everything is important) and pace and sequence events. Secondly the leader must protect, orient, provide norms and reestablish values. Thirdly the leader should have presence and poise and should have the emotional capacity to withstand ambiguity, frustration and anguish. She will be observed by colleagues to see if she has the intestinal fortitude to hold steady and tackle the tasks ahead.

Anatomy of a Change Initiative

The fear of change (Metathesiaphobia) is often a result of the fact that the benefits of the change are not clearly established or realized while the loss that change evokes is immediately felt. In addition there will be many who cling to the "old" way of doing things, while there may few supporting the new initiative because the outcome may not be certain. The leadership challenge lies in defining a compelling vision, setting and creating an urgency (not anxiety) around the change imperative, building a guiding coalition, communicating, addressing obstacles, and celebrating and noting short term wins (8). An adaptation of this universal approach has been described both in a Curricular Change initiative at UCSF (29) and in moving to Universal Start Times in the Perioperative environment in our own institution (30). The Table below is adapted from the latter work.

Table: Ingredients for a Successful Change Initiative

Development of trust
- Information Sharing
- Shared Values
- Role Modeling Change

Development of compelling vision
Creating an urgency.
Guiding coalition.
Communication
Short-term wins: monitor progress.
Don't declare victory too soon.

Parallels in Industry with respect to the Perioperative Setting

As there is little to no literature on how leadership principles might be applied to the perioperative setting, the aviation industry may serve as an example. This is an industry, (similar to the perioperative arena) that functions in a time pressured, stressful and highly regulated environment where a premium is placed on safety and quality. South West Airlines is a well known example of this industry. While many have filed for bankruptcy in the past or consolidated, Southwest Airlines, has remained profitable year after year and is considered one of the ten safest airlines. (31) *FORTUNE* listing Southwest Airlines as number five among America's Top Ten most admired corporations and the airline was named to *Business Week*'s first ever list of "Customer Service Champs" while being ranked as one of the top 50 Best Places to Launch a Career (32).

The leadership and management practices of this airline have been dissected to evaluate the leadership style of its founding CEO, Herb Kelleher. Herb has created a "culture of *commitment*" practicing as a servant leader with a very distinct customer orientation, both outward (passengers) and inward, to each employee (33). The airline has a clear *vision/mission*, "to the highest quality of customer service delivered with a sense of warmth, friendliness, individual pride and Company spirit" (32). Strong core *values*; "maintain principles, while changing practices" (33) and competitive *strategies*; by focusing on a point to point service, using a single plane type (737's) for efficiency.

Application of principles to Perioperative Medicine

It must be clear a cook book recipe for Leadership in Perioperative Medicine cannot be provided as each institution is different. Nevertheless a focus on Key Areas of Concern and Principles of Leadership may be of advantage (35).

Creating the Environment

Creating an environment for work that is collegial, respectful, equitable, safe (for patient and practitioner), adaptable and goal oriented, is a paramount concern for leadership. In order to create and sustain this environment, leadership does well to consider all participants volunteers. Leaders can and should:

(1) Be visible and role model the established values.
(2) Build trust and trustworthiness through transparency and their own actions
(3) Be ever mindful that their emotional style sets the tone for the environment
(4) Be goal oriented
(5) Be prepared to deal with problems, timeously and decisively
(6) Communicate, communicate, communicate, using all media at their disposal.

Leadership shared at all levels

The view that there is a single leader at the top from whom all initiatives flow is insufficient to deal with today's complex perioperative environment. Leadership is about relationships (13). Thus, Leadership is created together. To be effective, leadership needs to occur at multiple levels (8). Leadership is an interchangeable phenomenon, "now you lead, now I lead" depending on the circumstance and the particular skill set required.

Leaders can and should:

(1) Foster leadership at appropriate levels
(2) Cede responsibility (and accountability) to allow leadership development

Building interdisciplinary teams

The case studies of 16 cardiac surgical teams illustrates the strength of interdisciplinary team development vs. the "command and control approach".

Leaders can and should:

(1) Decide where processes can benefit from the development of Teams
(2) Create an environment of psychological safety, allowing "learning in action" for such team development

Change management,

Leadership is about managing constructive change. As Mahatma Gandhi said, the Leader should "Be the change you want to see." Leaders can and should:

(1) Identify and articulate clearly the need for change and the advantages of the future state
(2) Establish what Adaptive Change is required and what values may need to be addressed to effect this
(3) Recognize that change is "loss"
(4) Set Priorities, re-iterate values, protect and support
(5) Maintain an urgency while regulating the pressure
(6) Recognize short term wins
(7) Don't declare victory, too soon

Conclusion

The concepts of leadership are universal and can be applied with advantage to the perioperative setting.

Leaders learn best by leading and learn best in the face of obstacles.
As weather shapes mountains, problems shape leaders."
Warren Bennis (9).

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Perioperative Management of Pulmonary Arterial Hypertnsion and RV Dysfunction.

Eric Jacobsohn, MBChB, MHPE, FRCPC, Professor, University of Manitoba, Winnipeg, CANADA

Key points:

- The physiology of patients with PAH involves complex cardiopulmonary interactions.
- PAH patients are at high risk for complications and ideally should be managed in specialty centers. If it is a "have-to-do" scenario, summon help from someone versed in managing perioperative PAH.
- Complications can often be prevented by understanding the conditions causing perioperative deterioration.
- Many monitoring modalities are important in at risk patients. The choice is patient/ situation specific. The CVP is a very useful monitor, as a low CVP generally means that the RV is "coping", while a high CVP (>20) likely portends trouble. In high risk patients, continuous monitoring of RV function with echocardiography and PA pressures with a PA catheter may be helpful. Continuous RV pressure monitoring from the RV port of the PAC is a simple and invaluable beat-to-beat RV function.
- Systemic hypotension, from any cause, is disastrous in patients with PH. It causes further displacement of the intraventricular septum towards LV, globular dilation of RV, further RV dysfunction of the already compromised RV, and reduced coronary artery perfusion. This leads to a rapid and lethal spiral.
- Emergency vasopressors must be must be in-line and "ready to go" when caring for these patients, and should start while searching for the cause of the hypotension. Use incremental boluses of vasopressin, starting with boluses of 0.2 to 0.4 U (20U vasopressin in 100ml diluent = 0.2U/ml), rapidly escalating if needed, and start an infusion of 2.4U/hr. (12ml/hr. of aforementioned solution). Also start a norepinephrine infusion at 0.05mcg/kg/min, and titrate as required.
- The cause of acute RV failure in the setting of PH is often multifactorial and includes: factors that exacerbate the existing PAH (increased PVR), change in RV function due to changes in volume, rate, rhythm, septal position, and contractility. The causes must be immediately treated.
- PVR is dependent on many factors that can be manipulated in the perioperative period. Most acute increases in PVR can be remedied by the non-pharmacological methods, especially those factors that affecting functional residual capacity and PVR. An inhaled pulmonary vasodilator must be immediately available if these measures are not successful.
- Delay in treating acute RV failure causes rapid organ system failure due to "the double hit" phenomenon.
- Institution of acute mechanical circulatory assist (peripheral VA ECMO) must be available in very high risk cases. It must be started early in the cycle of RV deterioration, before the onset of organ injury.

Introduction

Pulmonary hypertension (PH) and the associated right ventricular (RV) dysfunction are increasingly being encountered in the perioperative period. Managing these patients is challenging as they have a high morbidity and high mortality. Understanding of the pathophysiology of PH and the related RV dysfunction allows the practitioner to anticipate, prevent, and manage these patients. Normal systolic, diastolic, and mean PA pressures are 25, 10, and 15 mmHg, respectively; normal range for pulmonary vascular resistance (PVR) is 0.9–1.4 Wood units or 90–120 dynes • s • cm–5. PVR = (ΔP)/flow, where ΔP represents the mean pulmonary artery pressure (mPAP) minus the left atrial pressure (LAP), and flow is the cardiac output (CO). The gradient between mPAP and LAP is the transpulmonary gradient (TPG). If the TPG is elevated, there is an increase in PVR; on the contrary, if the TPG is not elevated, the increase in mPAP is caused by an elevation in LAP resulting from left heart pathology. Therefore, only three physiological factors cause a rise in mPAP: (1) ↑ LAP, (2) ↑pulmonary flow (congenital heart disease with L to R shunt), and (3)↑ PVR (caused by pulmonary parenchymal/airway disease, hypoxia, interstitial lung disease, thromboembolic disease, or idiopathic pulmonary artery hypertension (PAH).[1] Because of pulmonary vascular remodeling in the long run, even factors 1 and 2 could eventually lead to an ↑ PVR, and the associated rise in mPAP will reflect both an ↑ in LAP as well as an eventual elevation in PVR. For example, patients with mitral stenosis who have an ↑ mPAP solely because of elevated LAP (without increased PVR, i.e., early or "reversible" PH) usually have an uncomplicated mitral valve replacement with little risk of RV failure after surgery. In comparison, patients with mitral valve stenosis associated with a preoperative ↑ in LAP, mPAP, and PVR (secondary to pulmonary vascular remodeling, i.e., "fixed" PH) may have severe RV failure after mitral valve replacement, which could lead to

difficulty in weaning from bypass. Acute-on-chronic ↑in PVR are common in the perioperative period and can lead to acute decompensation in RV function. Some of the factors responsible for acute exacerbations in PVR are hypoxia, hypercapnia, acidosis, hypothermia (shivering), ↑ sympathetic tone (pain, anxiety), and exogenous or endogenous pulmonary vasoconstrictors such as catecholamines, serotonin, thromboxane, and endothelin. Early recognition and reversal of these causes of acute deterioration can be lifesaving. This educational session will be focus on the periop management of those patients with PAH/RV failure, and not that related to left heart disease.

The definition and classification of pulmonary hypertension The diagnosis patients with PAH is largely based on guidelines developed during the World Symposia on PH (WSPH). Normal resting mPAP is 14 ± 3 mmHg, with an upper limit of 20 mmHg. The significance of mPAP between 21–24 mmHg is unclear. The European Society of Cardiology and Respiratory Society define precapillary PH as a persistent increase in mPAP ≥ 25 mmHg at rest as assessed by right heart catheterization in the setting of a normal pulmonary capillary wedge pressure (PCWP) of ≤15 mmHg, PVR ≥3 Wood units, and normal or reduced cardiac output. They define postcapillary PH as a persistent increase in mPAP ≥25 mmHg at rest as assessed by right heart catheterization (RHC) in the setting of an increased PCWP ≥15 mmHg, PVR ≥3 Wood units, and normal or reduced CO.[2]

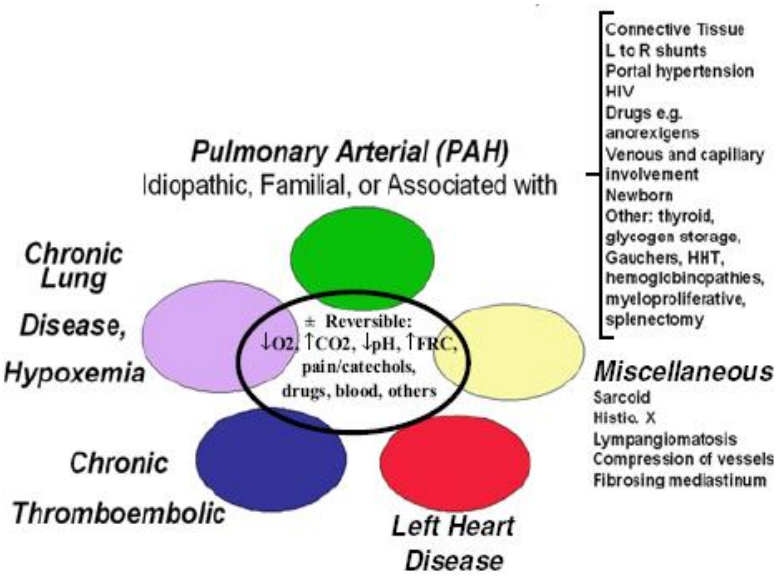


Figure 1: WHO classification of pulmonary hypertension.

The definition of PH according to the American College of Cardiology/American Heart Association 2009 Expert Consensus Document on Pulmonary Hypertension is a measurement, by RHC, of a resting mPAP ≥25 mmHg, PCWP/LAP ≤15 mmHg, and PVR ≥3 Wood units.3 PH has undergone several reclassifications over the past 20 years (**Figure 1**).[4] There are 5 major categories: (1) pulmonary arterial disease (PAH), (2) left heart disease, (3) lung disease with hypoxemia (4) chronic thromboembolic PH (CTEPH), (5) unclear and/or multifactorial causes. Because this classification is not based on a physiological approach, classification into *precapillary, postcapillary*, and *mixed* PH may more useful in the perioperative period **(Figure 2).**

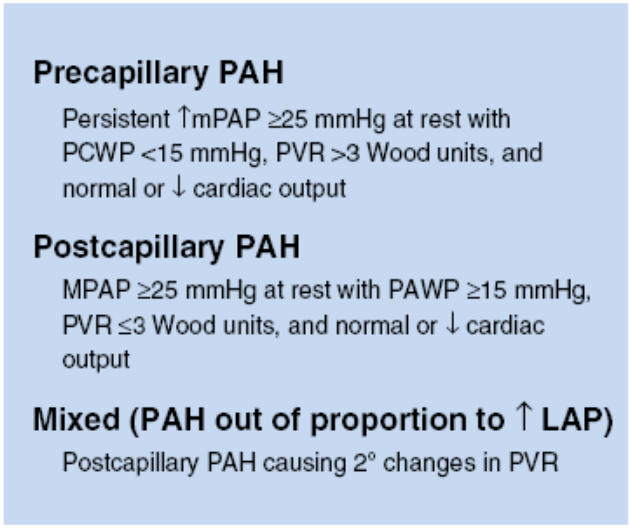


Figure 2: Physiological classification of pulmonary hypertension. (PAH = pulmonary arterial hypertension; mPAP = mean pulmonary artery pressure; LAP = left atrial pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance)

Pathogenesis

PH is a syndrome resulting from a pathological increase in PVR that leads to restricted flow through the PA circulation and, ultimately, RV failure. The loss of vascular cross-section due to remodeling is the predominant reason for the rise in PVR; however, excessive vasoconstriction may be a significant contributing factor in about 20% of patients.[5] The vasculopathy, which predominantly affects small pulmonary arteries, consists of intimal hyperplasia, medial hypertrophy, adventitial proliferation, thrombus in situ, and inflammation. The causes are shown in **Figure 1.**

Diagnosis and investigations

Many of the patients presenting in the periop will have had a full workup and will be on the therapy. The most common presenting symptoms are related to cardiopulmonary limitation: fatigue, dyspnea, chest pain, syncope, palpitations, and lower extremity edema. Syncope is ominous and a poor prognosis. Signs of PH and RV are: tachypnea, tachycardia, distended neck veins, RV lift, TR murmur, RV S3 gallop, hepatomegaly, ascites, and lower extremity edema. ECG, chest x-ray, and transthoracic echocardiogram (TTE) display signs suggestive of PH. A TTE is essential to assess severity of PH/Rv dysfunction, as well as excluding heart disease. CTEPH must be excluded; 50% of these patients have no history of PEs. A right heart cath will delineate the hemodynamic profile and assess response to vasodilators. Targeted serology is done to delineate possible systemic disease. Liver and kidney functions assess the severity of chronic RV failure. Polysomnography is done when sleep apnea when suspected.

Long-term therapy

Treatment goals include efforts to improve functionality (6-minute walk test), lowering mPAP, normalizing CO, slowing progression, and improvement in survival.[3] Low-level aerobic exercise is encouraged. Oxygen therapy is indicated if resting saturation is < 90%. Ideally, pregnancy should be avoided. Judicious use of diuretics and a sodium-restricted diet are indicated in RV dysfunction. Calcium channel blockers are indicated in only a small group of patients with idiopathic PAH patients. BIPAP may improve PVR and RV function in patients with OSA. There are 5 classes of drugs: prostanoids (IV, SC, inhaled, and oral), phosphodiesterase inhibitors (PO), endothelin antagonists (PO), guanylate cyclase stimulants (PO), and calcium channel blockers (PO) **(Figure 3**).

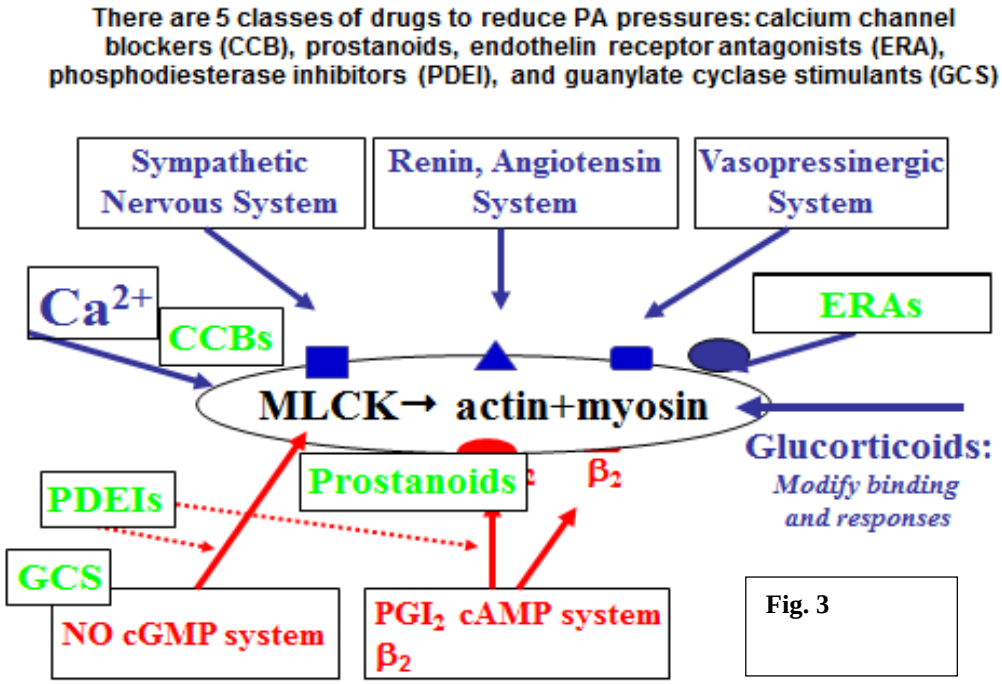


Figure 3: Classes of drugs for treating PHT. (PDEI = phosphodiesterase inhibitors; ERA = endothelin receptor antagonists; MLCK = myosin light chain kinase; GCS = guanylate cyclase stimulantors; PGI2 = prostacyclin; cAMP = cyclic AMP; cGMP = cyclic GMP; CCB = calcium channel blocker)

The agent chosen is dependent of the disease severity, availability, cost, medical support in a particular community (ability to deliver home IV infusions), patient preference, etc. Functional class IV were often stabilized with IV prostanoid therapy (prostacyclin, treprostinil), but less invasive therapies have rapidly evolved. Treprostinil can be given subcutaneously, and iloprost can be given by inhalation. Oral prostanoid therapy is now a reality. Many patients eligible for prostanoid therapy do not receive it due to the high cost. Although tachyphylaxis occurs, the beneficial effects of prostanoids are sustained for years and many patients have been removed from heart-lung transplantation lists. Activation of endothelin receptors causes pulmonary vasoconstriction; the oral endothelin receptor antagonists (bosentan, ambrisentan, macitentan) are also used as first-line oral therapy in less severely symptomatic patients. Oral phosphodiesterases(PDE) inhibitors (sildenafil, tadalafil) are also first line agents in less severely symptomatic patients. PDE-3 and -5 are the enzymes that metabolize cAMP and cGMP respectively, the second messengers of prostacyclins and NO. PDE augment cAMP- and cGMP levels, causing vasodilation and decreased PVR. A new class of oral agent called the soluble guanylate cyclase stimulators (riocuguat) increases the production of and sensitivity to cGMP. Combinations of the various agents are also used in severe cases.

Patients whose PH is associated with Eisenmenger syndrome (R to L shunt) generally have superior survival rates compared to patients with idiopathic PAH, mainly because of decompression of a pressure-overloaded RV, improved LV filling, and a resulting increase in CO.[8] Atrial septostomy is considered a palliative procedure and may be a bridge to lung or heart-lung transplantation.[8] The shunt causes a decrease in systemic arterial oxygen saturation that is compensated for by increases in CO and systemic oxygen delivery. Pulmonary endarterectomy is an important therapy for some patients with CTEPH. Identification of these patients is important, since CTEPH is underdiagnosed has a poor prognosis if untreated.[9] Bilateral lung transplantation (and occasionally heart-lung transplantation) is the final option for a minority of patients in whom medical therapy has failed or present in an advanced stage. Only approximately 4% of lung and combined heart/lung transplants performed annually worldwide are for patients with PH.[10] Extracorporeal support is an important rescue option for acute RV failure

caused by reversible causes e.g. massive PE and others. VA ECMO has also been used as a bridge to lung transplantation, support after lung transplant, treatment of severe reperfusion pulmonary edema after pulmonary endarterectomy, and for RV failure unresponsive to medical therapy.[11,12] Patients with end-stage RV failure due to idiopathic PAH have generally done poorly with RV assist devices, as the increased flow in a high resistance circuit damages the pulmonary microcirculation, causing hemorrhage.

Long term prognosis

Predictors of poor prognosis include advanced NYHA Functional Class 3 or 4, rapid symptom progression, poor exercise capacity, significant RV dysfunction, low CO, elevated brain natriuretic peptide, and an associated diagnosis of scleroderma. The best survival rates are seen in patients with congenital heart disease associated with PH. The natural history of idiopathic PAH reveals a median survival of 2.8 years with 1-, 3-, and 5-year survival rates of 68%, 48%, and 34% respectively.[13]

Perioperative RV failure in patients with PAH

Although often preventable, acute decompensation of patients with PAH during the periop period is common, may be fatal, and results in acute RV cardiogenic shock. As recent as 2002, patients with Eisenmenger syndrome undergoing cesarean section had a mortality of 70%.[14] In 2005, patients with PAH undergoing liver transplantation had a reported mortality of 80%.[15] The perioperative risks associated with PAH have improved substantially, likely as a result of better medical management, risk stratification and periop management **(Figures 4 and 5)**.

Emergency procedures, ASA class >2, intermediate- or high-risk surgery, longer duration of surgery (>3 hours), CAD, chronic renal insufficiency, history of PE poor functional class have been identified as predictors of morbidity and mortality after non-cardiac surgery. High-risk surgical procedures are: significant systemic inflammatory response, blood loss, high possibility of CO2 (laparoscopic), fat or cement emboli, and lung resection. Surgery should be delayed, if possible, if the PVR is largely fixed during vasodilator testing, or if there is moderate to severe PAH with significant RV dysfunction. Important factors that impact decisions are also shown in **figure 4**. Attempts must be made to optimize PVR before surgery, including maximizing medical therapy and preventing conditions that may cause acute deterioration. Patients on chronic PAH therapy should continue their regimen throughout the perioperative period, as discontinuation can precipitate an acute PAH hypertensive crisis. Intravenous prostacyclin has potent antiplatelet properties and changing to inhaled therapy preoperatively should be considered, especially if increased blood loss is anticipated. In patients not on PAH-specific therapies, a preoperative RHC, vasodilator trial and PAH-specific therapy should be started. Acute perioperative decompensation and the subsequent potentially lethal RV failure are often under-recognized or misdiagnosed.

Patient risk factors
– History PE, CAD, CKD
– NYHA/WHO class ≥2
– Right axis deviation on ECG
– Echo: Right ventricular hypertrophy
– High CVP, RAP, RVSP/SBP >0.66

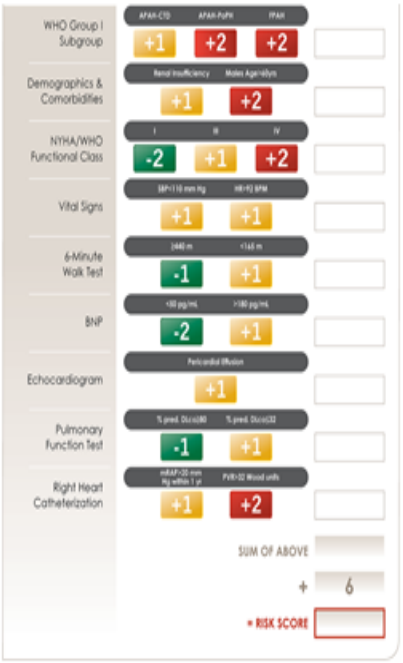
Operative risk factors
– Emergency surgery
– Intermediate-or high-risk surgery
– Higher ASA class
– Long duration of surgery
– Significant intraoperative vasopressor use

MORBIDITY 15–40%
– **Higher in thoracic and orthopedic surgery, laparoscopic**

MORTALITY 7–10%
– **Higher in OB ± 17%**[14]

– What is the perioperative risk?
– Is this the least invasive procedure?
– Is the patient adequately prepared?
– Is the patient at a PH center?
• Is the perioperative team experienced with this disease?
– Type of anesthesia?
– Open vs. minimally invasive (laparoscopic, other)?

Figure 4: Perioperative risk factors.



Reveal risk score:
0-19
Low: <7
Average: 8-9
Moderate high:10
High: 11
Very high: >12

Figure 5: REVEAL risk score.[6]

Shock caused by acute RV failure is schematically presented in **Figure 6 and 7;** it has a poorer prognosis as compared to LV. RV failure (low end-organ inflow pressure due to reduced LV stroke volume and high end-organ outflow pressure due to elevated RA pressure) has a worse prognosis than shock due to acute LV failure (only low end-organ inflow pressure) because of the *"double-hit"* on end-organs, leading to rapid multiorgan system failure. In addition, elevation in RA may cause hypoxemia by R to L shunting across a PFO. It is important to note that TR is common in acute and chronic RV failure; hence, thermodilution CO are not reliable at all. However, PA pressure measurements are useful to monitor in selected patients to assess response to vasodilators, inotropes, vasopressors and to assess the very helpful RV pressure curves (see below). Many issues in the perioperative period, some of them "minor" by themselves, can critically affect the outcome of these patients. These include, among others, the timing of extubation, meticulous management of mechanical ventilation, the surgical acumen, fluid and electrolyte shifts, balancing the positive vs. negative effects of transfusion, intravascular volume optimization, acid-base optimization (pH >7.4, PaCO2 30–35 mmHg, PaO2 >100 mmHg), avoiding hyperchloremia, temperature control, optimized analgesia, and early restarting of noninvasive ventilation.

Prevention and treatment of perioperative complications

1. *Optimize heart rate, rhythm*

Restoring and maintaining SR is critical for optimal filling of a hypertrophied/dilated RV. Because of the association of RV failure with TR, higher heart rates (80–100 bpm) may be desirable to reduce end-diastolic volume. Because an increase in RV stroke volume is limited by the increase in RV afterload, it is best to avoid bradycardia (RV CO is rate dependent). Early cardioversion should be considered; the loss of SR may lead to acute RV shock. If pacing is possible, atrial or AV pacing may improve RV cardiac output. RV pacing is usually poorly tolerated. Electrolytes must be optimized to prevent arrhythmias. Efforts made to mitigate mechanical irritation of the cardiac chambers by central lines (e.g. make certain the distal end of the central venous catheter does not enter the RA).

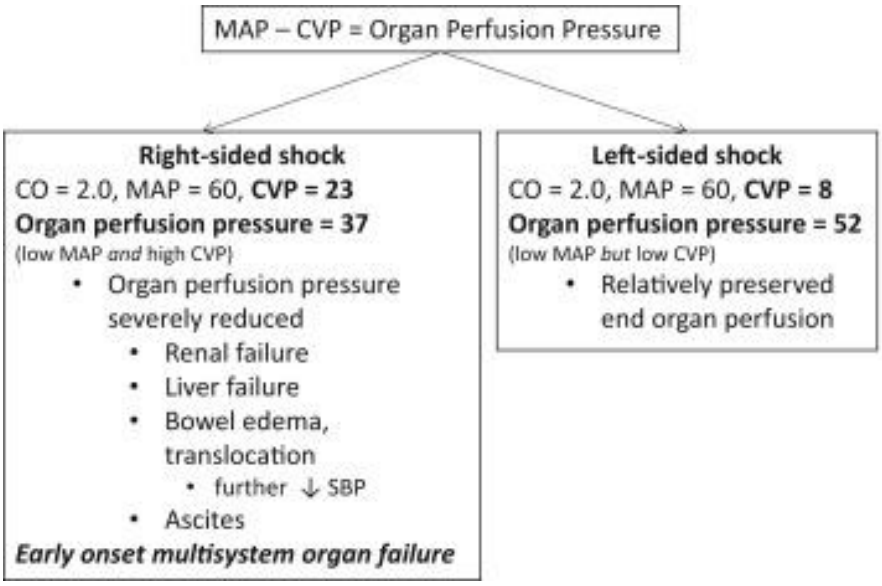


Figure 6: Comparison of left and right-sided cardiogenic shock.[1]

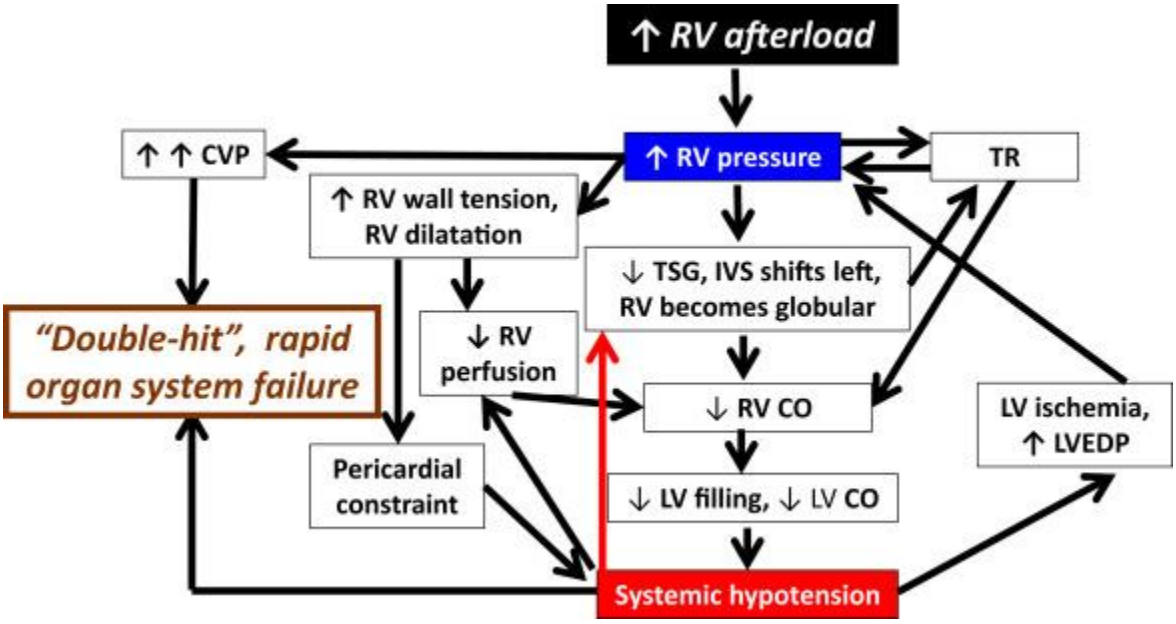


Figure 7: The rapid and lethal cycle of RV cardiogenic shock.[1] The "double-hit" consists of systemic hypotension and elevated central venous pressure (CVP) resulting in organ system failure. An increase in RV afterload or volume causes increased wall tension, septal shift due to a reduced trans-septal gradient (TSG). Tricuspid regurgitation (TR) occurs, exacerbating RV volume overload. The increased wall tension decreases right coronary artery (RCA) perfusion, resulting in ischemia. The TSG reduction reduces LV compliance, decreases preload, and results in hypotension)

2. *Optimize RV filling*

Periop CVP monitoring is crucial. In general, if the CVP is low, the RV is "coping", even if the PA pressure and PVR are elevated i.e. the RV is "primed" (hypertrophied) as a result of being exposed to high PAP/PVR over time, or it is

truly underfilled. On the other hand, an elevated CVP may imply a failing RV, especially when accompanied by ↑ size of V waves (worsening TR) and ↓ in PA pressure and CO (by clinical signs, pulse pressure, but no thermo-dilution). The compromised RV will tolerate neither hypovolemia nor overfilling; therefore, an optimal position has to be determined and maintained on the (compromised) RV Frank-Starling curve. Because the RV is mainly a "volume chamber," it is less dependent on preload than the LV. Thus, for a given ↑ in preload, a smaller ↑ in SV is expected. However, because the normal RV it is thin walled, the RV is much more afterload dependent than the LV, and RV cardiac output↓significantly with an acute↑in mPAP. Past teachings have often suggested that the RV be filled aggressively to passively increase pulmonary blood flow and CO. This may hold true when the PVR is normal (Fontan physiology), but not when it is high i.e. the case of patients with PH. Excess volume loading in these circumstances will result in acute RV distention, ↑ TR, further R to L shift of the interventricular septum, and impaired LV filling, leading to a ↓ in LV SV and CO . The resultant drop in systemic blood pressure causes decreased RCA perfusion as well as a decline in the transeptal gradient (TSG), and eventually hemodynamic collapse. This is especially true once the CVP reaches 15–20 mmHg. Assessment of optimal RV filling can be very difficult. Options include a fluid bolus (500 mL of Lactated Ringer's solution) or autotransfusion (by elevation of legs). Ongoing fluid boluses are indicated if leg elevation causes a modest (2–5 mmHg) ↑ in CVP and corresponding ↑ in PCWP, CO, and/or MAP; an ↑in only the CVP (with minimal or no change in PCWP, CO, or MAP) likely indicates RV distention and precludes further fluid boluses. A relatively underfilled RV is likely the lesser of the two evils. Bedside TTE is invaluable. If TTE is not possible, TEE should be considered if intubation was to be part of the periop plan. In patients with a PAC, monitoring RV filling pressures through continuous transducing of the RV pressure tracing is an underused but invaluable (see below). The assessment of volume status is therefore a multimodal approach; no one approach is superior.

3. *Maintain RV myocardial performance* (**Figure 8**)

This includes maintenance of RV coronary perfusion pressure and RV inotropy. Normally, RV coronary perfusion occurs during systole and diastole. However, as the PVR and RV systolic pressure ↑, flow through the R coronary artery occurs mainly in diastole, similar to left. RV subendocardial ischemia caused by myocardial oxygen supply-demand imbalance is common in PAH.

	RV Inotropy	PVR (with sPsA vasodilator)	SVR	TSG	TSG + sPA vasodilator
PDE_3I	++	↓↓	↓↓↓	↓↓	
β-agonists	++	↓	↓	↓	
Ca^{2+} sensitizers	++	↓↓	↓↓↓	↓↓	
α-agonists	–	(↓↓)	↑↑	±	↑
AVP	-	(↓)	↑↑	↔ or ↑	↑
Inotrope + AVP	++	(↓↓)	↑	↔	↑
Inotrope + NE	++	(↓)	↑↑	↔ or ↑	↑

Figure 8: The effect of vasoactive agents in RV cardiogenic shock. (TSG = trans-septal gradient; sPA – selective PA vasodilator; NE = norepinephrine; AVP = arginine vasopressin)

Therefore, systemic hypotension and excessive ↑ in RV systolic pressure, contractility, and HR must be avoided. When acute RV failure is suspected, the systemic blood pressure must be increased immediately to ensure adequate RCA perfusion and restoration of TSG. This is achieved by optimizing volume status and with early use of norepinephrine and vasopressin. Accumulating clinical experience, as well as animal data, suggests that

vasopressin causes little or no ↑in PVR, whereas norepinephrine its alpha agonism, does ↑ PVR. Vasopressin binds to peripheral V1 receptors and causes systemic vasoconstriction, while stimulating NO release and vasodilation in the pulmonary circulation. The choice of anesthetic technique (GA vs. regional) and the anesthetic agents used are much less important than understanding the physiological perturbations. All anesthetic agents and techniques cause varying degrees of myocardial and autonomic nervous system depression. In this regard, volatile agents, propofol, thiopental, narcotics, ketamine, and etomidate can all be used in the appropriate manner. Contractility may need to be enhanced in the acutely failing RV with either a β-adrenoreceptor agonist (dobutamine) or PDE-3 inhibitor (milrinone). If the ↑ in RV CO not offset the ↓ in SVR, blood pressure will decrease, resulting in ↓ RCA perfusion and a ↓ TSG. The combination of low-dose dobutamine and low-dose milrinone is synergistic in inotropy and has fewer negative effects on SVR.

Invasive and non-invasive monitoring is helpful to guide management **(Figure 9)**. CVP is crucial monitor. If CVP is low, RV cardiogenic shock is unlikely. However, excessively high CVP (venous congestion) contributes to decreased vital organ perfusion. Temporal trends and response of CVP to fluids and inotropes is a seminal part of managing RV shock. Efforts should be made to decrease CVP to < 20 mm Hg. The PA catheter is very useful in patients with RV shock. PAP response to therapy can be monitored; both an increasing or decreasing PAP can be signs of worsening problems. An increasing PAP and decreasing CVP might indicate an improved CO flowing through the high PVR system. A decreasing PAP and increasing CVP is indicative of a very low CO.

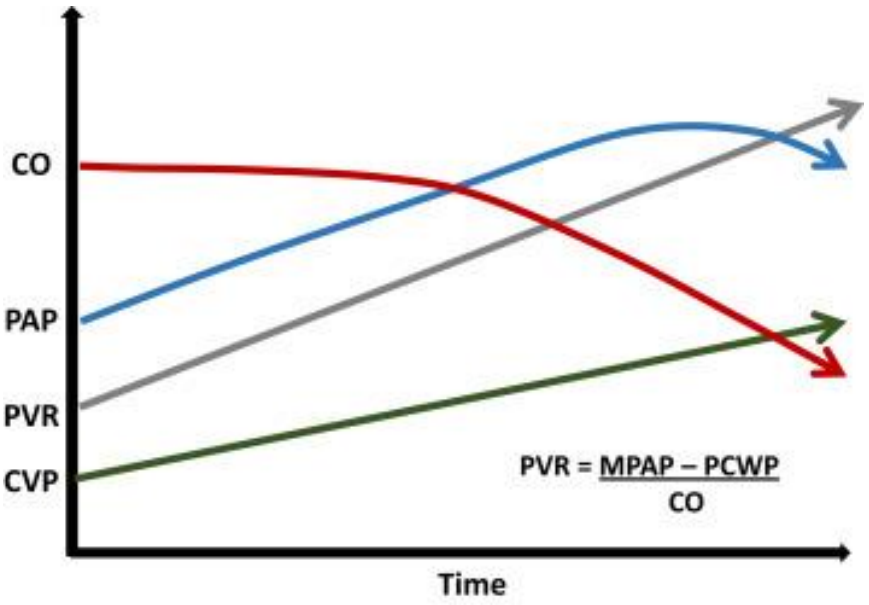


Figure 9: Invasive and non-invasive monitoring in RV shock.[1] Relationship between cardiac output (CO), pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR), and central venous pressure (CVP). As pulmonary pressures increase, CO will decrease. MPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure)

Mixed venous saturation is a valuable surrogate for CO, but will be misleading in presence of intra-cardiac shunting. PH and RV distention are invariably associated with TR. Acute TR underestimates thermodilution CO (tdCO) when the CO is high, and overestimates when CO is low. Mild TR has minimal effect, but severe TR underestimates tdCO. Consequently, tdCO should not be used in RV cardiogenic shock. Monitoring overall RV function with continuous RV pressure transduction through the RV port of the PAC is invaluable **(Figure 10)**, which shows progression form a flat (A) diastolic pressure relationship (i.e. a normal, compliant RV), to the non-compliant square-root type waveform in the failing, pressure-overloaded RV.

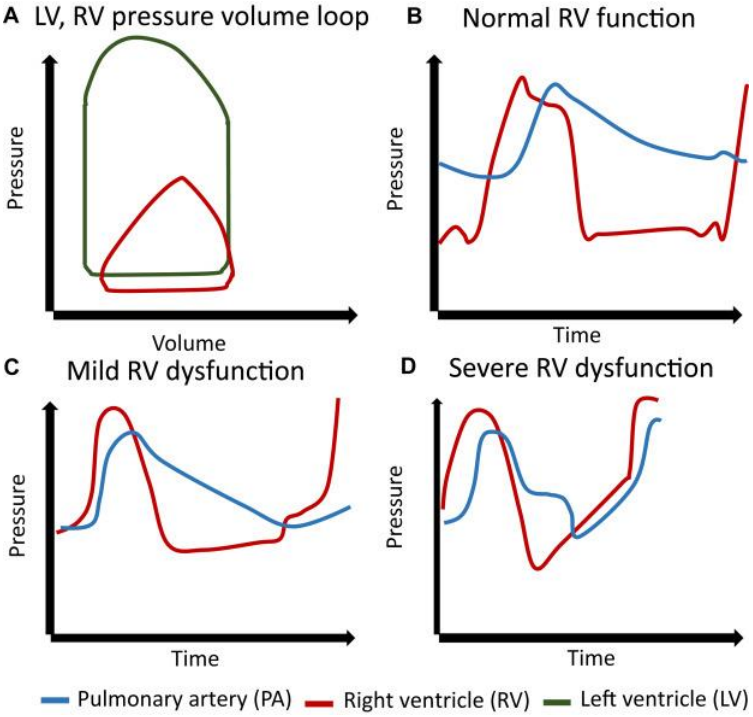


Figure 10: Monitoring the RV port of the PA catheter.[1]

3. *Maintain the TSG and RV geometry*

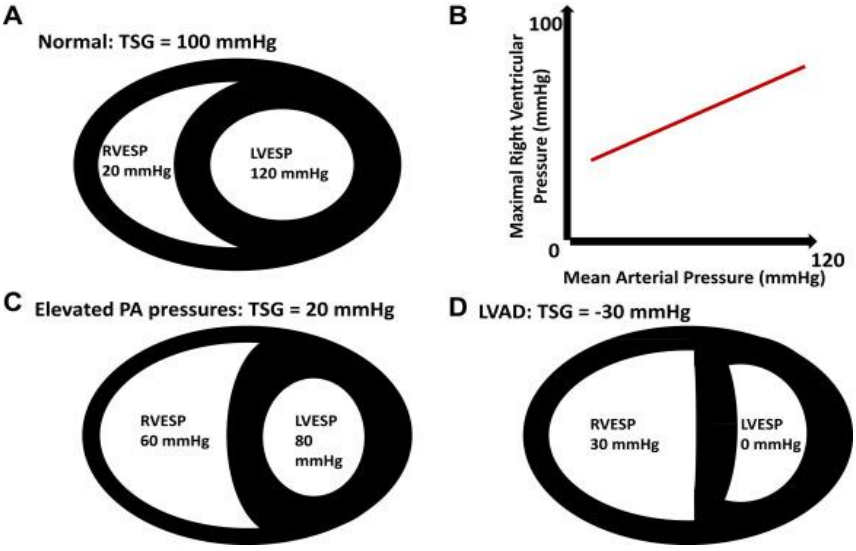


Figure 11: The critical concept of trans-septal gradient.[1] (RVESP = right ventricular end systolic pressure; TSG = trans-septal gradient; LVESP = = left ventricular end systolic pressure; LVAD = left ventricular assist device)

At normal systolic pressure (RV 20 mmHg, LV 120 mmHg, **Fig 11A**), there is a large TSG (TSG = 100 mmHg) which is responsible for bulging of septum towards the RV (i.e. the normal configuration of the IV septum); this provides a "base: for the free wall to contract against. The septal component accounts for more than 50% of RV systolic function. It is important to note that the peak pressure that an RV can develop is proportional to systolic blood pressure (**Fig 11B**), and hence maintaining a high systolic pressure is a crucial aspect of managing a failing RV. Therefore, conditions that reduce LV systolic pressure (systemic hypotension) or increase RV systolic pressure will reverse the TSG and severely compromise RV function. In patients with PHT, the RV pressure in increased, the systemic pressure is often reduced because of reduced CO, and hence the TSG is very reduced **(Fig 11C)**. This

situation is very important when patients are implanted with an left ventricular assist device (LVAD, **Fig 11D**), when the LV pressure becomes very low (close to zero) and hence the TSG become negative; this is an important reason why there is such a high incidence of RV failure after LVAD placement. This reduction in the TSG causes a change in the orientation of cardiac myofibrils. The normal helical nature of myocardial fibres and bands will unfold and lead to a globular, dysfunctional RV **(Figure 12).** Septal function be compromised because of misalignment of the obliquely oriented septal myofibrils to a transverse configuration, resulting in less contractile force, but the free wall loses its sturdy "base" as the distance between the free wall and the septum increases (the result of leftward septal bowing). In order to restore the TSG, the PVR needs to be reduced and LV systolic pressure needs to be aggressively maintained or increased. This is critical!

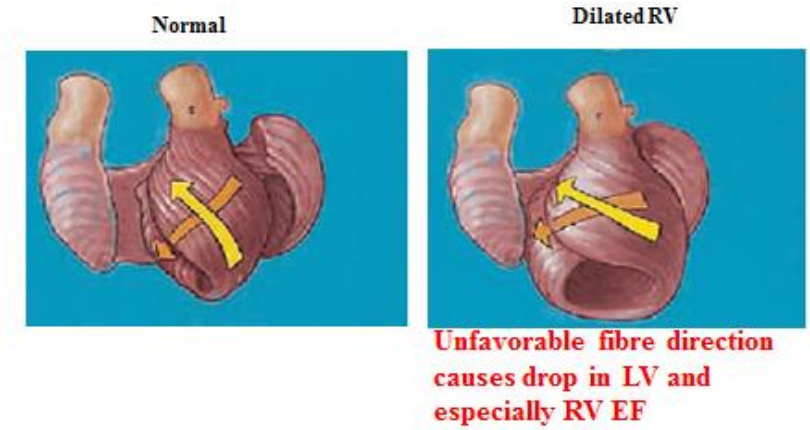


Figure 12: The normal helical orientation of cardiac fibers(A), and the unfolding of the helical orientation of the fibers as a result of RV dilatation (B), and reduced RV ejection fraction.[5]

4. *Reduce the PVR*

Perioperative hypoxemia, hypercapnia, atelectasis, pleural effusions, hypothermia, fluid overload, pain, and anxiety all cause acute rises in PVR with resultant RV decompensation. Patients on chronic therapy for PAH should continue established treatment. Functional residual capacity (FRC) must be carefully maintained, as both hyperinflation and atelectasis cause an increase in PVR. The important relationship between lung volume and FRC during mechanical ventilation is U - shaped with PVR the lowest at FRC **(Figure 13).** At low lung volumes, hypoxia and hypercapnia cause hypoxic pulmonary vasoconstriction; on the other hand, hyperinflation causes compression of intraalveolar vessels with a resultant increase in PVR in both circumstances. PEEP >15 mmHg also leads to an increase in PVR. In contrast to systemic arteries, PAs constrict with hypoxia (Euler-Liljestrand reflex) and dilate with hyperoxia. Therefore, perioperative ventilation strategies for patients with PH should incorporate high concentrations of oxygen, low TV (6 mL/kg of predicted weight), a respiratory rate sufficient to achieve mild hypocapnia, and optimum PEEP (5–10 cmH2O). Early drainage of pleural effusions and recruitment maneuvers should be considered. Intravenous air or particulate material (precipitated drugs) should be meticulously avoided as R to L embolization through an open PFO may occur. In addition to the aforementioned physiological considerations, the PVR can be reduced by selective PA vasodilators. Unfortunately, none of common the IV vasodilators (NTG, SNP, CCB) are selective to not cause accompanying catastrophic systemic vasodilation; these agents could also potentially worsen hypoxia by inhibiting HPV. They should not be used. Similarly, IV prostacyclin should not be started during a crisis. Inhaled PA vasodilators are a crucial part of the management of the PAH/RV failure crisis when non-pharmacological methods have not corrected the increased PVR. Inhaled PA vasodilators improve V/Q matching and arterial saturation, which in itself decreases PVR and reduce PVR with much less systemic effects. Unfortunately, there are few outcome studies and most of their use is based on case reports, institutional experience and protocols. It is advisable that all centers that that deal with perioperative PH develop a plan for what inhaled pulmonary vasodilator they will use. One such proposed algorithm for their use is shown in **Figure 14**. Unlike the IV PA vasodilators, these agents have little effect on SVR. Inhaled nitric oxide (iNO) is a selective PA vasodilator (increases cGMP production) that is almost immediately inactivated by binding to Hb and is easy to use. Other agents that have been given by inhalation include sodium nitroprusside, nitroglycerine, prostacyclin, milrinone, iloprost, sildenafil, treprostinil and others. Rapid weaning of any inhaled agent can lead to rebound PAH. The powerful inhaled prostanoids treprostinil and iloprost are ideally suited to use in the perioperative period, although there is little published.

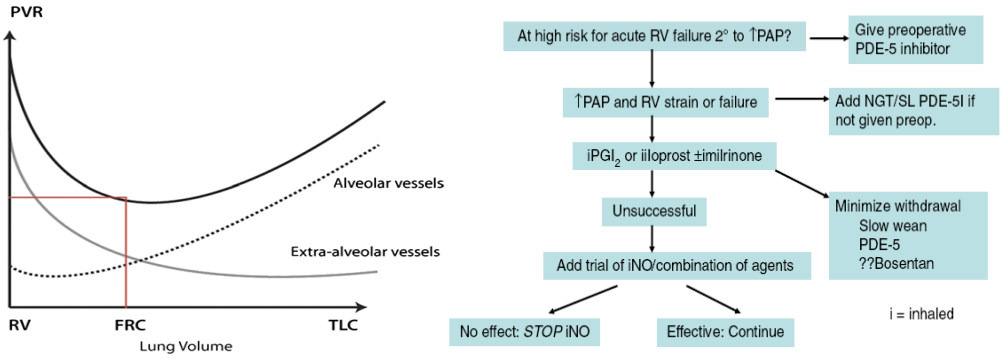


Figure 13: The relationship between lung volume and pulmonary vascular resistance.[4] (RV = residual volume; FRC = functional residual capacity; TLC = total lung capacity)

Figure 14: An algorithm for use of inhaled pulmonary artery vasodilator therapy in perioperative RV failure.[4] (PDE5I = phosphodiesterase 5 inhibitor e.g. sildenafil; NGT = nasogastric tube; SL = sublingual; NO = nitric oxide; iPGI2 = inhaled prostacyclin)

No one inhaled agent has been shown to have better outcomes. A combination of these agents, working at different receptor sites, may give have added benefit on PVR reduction. What is crucial is that the medical center has an algorithm for inhaled PA vasodilator use, that the practioners are familiar with it, and that the inhaled agents are immediately accessible. The PDE-5 inhibitor sildenafil has been used to manage acute RV dysfunction in heart transplant recipients, wean patients from iNO, reduce the duration of mechanical ventilation, and prevent pulmonary endothelial cell dysfunction after prolonged CPB. It also extends and potentiates the effects of iNO. Sildenafil has a significant first-pass metabolism, so the sublingual route (25-50 mg dissolves readily 1ml of sterile water) is an easy way to augment the inhaled agent.

5. *Mechanical circulatory assist*:

Peripheral VA ECMO is an option for acute RV failure that is not responsive to medical therapy and if the overall patient condition is conducive to this intervention. In the appropriate patient this should not be a "late" event but should rather be instituted before the onset of multiple organ system dysfunction. VA ECMO will serve as a bridge to recovery of RV function due to reversing the precipitating event and optimizing medical therapy, and some situations, as a bridge to a heart-lung transplantation. Pure RV assist devices have little or no role in acute RV cardiogenic shock due to a PH crisis as the high flows through a high resistance lung causes pulmonary bleeding. RV assist devices may of course have a significant role in RV cardiogenic shock due to mainly RV contractile dysfunction in the absence of severely abnormal pulmonary vascular resistance.

Conclusions

The periop management of patients with PAH and associated RV dysfunction is complex and requires a thorough understanding of the pathophysiology. Failure to make an early diagnosis of RV shock and institute the correct therapy will lead to high perioperative morbidity/mortality. The anesthesiologist must be aware of the potential treatment strategies including optimizing physiological parameters, use of selective PA vasodilators, inotropic support, and systemic blood pressure maintenance. Wherever possible, these patients should be cared for in specialty centers.

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ANESTHESIOLOGY 2017
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Continuous Peripheral Nerve Blocks, Liposome Bupivacaine, Cryoanalgesia, and (or?) Percutaneous Peripheral Nerve Stimulation in 2017

Brian M. Ilfeld, MD, MS (Clinical Investigation) **San Diego, California**

Continuous Peripheral Nerve Blocks

Introduction. Continuous peripheral nerve blocks (CPNB) consist of a catheter that is percutaneously inserted adjacent to a peripheral nerve, followed by local anesthetic administration *via* the catheter. Therefore, the terms "perineural local anesthetic infusion" and CPNB are often used synonymously. The maximum duration of a single-injection peripheral nerve block is currently 8-24 hours. Therefore, when a prolonged neural blockade is desired, CPNB provides an option.

Indications. CPNB is used to prolong intraoperative surgical anesthesia; treat intractable hiccups; induce sympathectomy and vasodilation to increase blood flow following a vascular accident, digit transfer/replantation or limb salvage; alleviate the vasospasm of Raynaud's disease; and treat peripheral embolism. CPNB can provide analgesia during transportation following trauma, or waiting for surgical treatment. Reports describe CPNB to treat chronic pain, such as intractable phantom limb pain, pain from terminal cancer and trigeminal neuralgia, and complex regional pain syndrome. However, the most common indication is providing postoperative analgesia (the only indication validated with randomized, controlled clinical trials [RCT]).

Most providers use CPNB exclusively for surgical procedures that are expected to result in pain not easily controlled with less-invasive analgesic techniques because there are intrinsic risks with the techniques,[1] or in patients with an intolerance to alternative analgesics (e.g., opioid-induced nausea). Although recommendations for the use of various catheter locations for specific surgical procedures exist, there is little published data specifically illuminating this issue. In general, axillary, cervical paravertebral (CPVB), infraclavicular, or supraclavicular infusions are used for surgical procedures involving the hand, wrist, forearm, and elbow (infraclavicular the most effective); interscalene, CPVB and intersternocleidomastoid catheters are used for surgical procedures involving the shoulder or proximal humerus (interscalene optimal risk-benefit ratio); thoracic paravertebral catheters are used for breast or thorax procedures; psoas compartment catheters are used for hip surgery; fascia iliaca, femoral, and psoas compartment catheters are used for knee or procedures thigh (occasionally hip surgery, although this is somewhat controversial); and popliteal or subgluteal catheters are used for surgical procedures of the leg, ankle, and foot (popliteal optimal risk-benefit ratio). CPNB has been described in hundreds of pediatric patients, although it is not as thoroughly validated as in adults.

Patient Selection. Little published data is available regarding the balancing of potential perineural infusion risks and benefits for patients with significant comorbidities. Investigators often exclude patients with known hepatic or renal insufficiency, in an effort to avoid local anesthetic toxicity. For infusions that may effect the phrenic nerve and ipsilateral diaphragm function (e.g. interscalene or cervical paravertebral catheters), patients with heart or lung disease are often excluded since *continuous* interscalene local anesthetic infusions have been shown to cause frequent ipsilateral diaphragm paralysis. Although the effect on overall pulmonary function may be minimal for relatively healthy patients,[2] practitioners must be aware of the possible related risks and be prepared to manage complications.

Catheter Insertion (Nerve Stimulation). Various catheter insertion techniques have been used, inducing paresthesias, eliciting a facial "click", and fluoroscopic guidance. However, most reports involve electrical stimulation. One common technique involves giving a bolus of local anesthetic *via* an insulated needle to provide a surgical block, followed by the introduction of a "nonstimulating" catheter. Many studies report a high success rate using this procedure,[3-6] but the catheter tip may be unknowingly misplaced during insertion.[7,8] To help counter this risk, the perineural catheter may be first inserted, followed by a local anesthetic bolus *via* the catheter itself.[9-12] Unfortunately, this technique requires waiting at least 15 minutes for block onset/failure, followed by removal of the catheter/dressing, re-preparation, and catheter reinsertion for failed a failed insertion.[13] In addition, a partial block is

possible suggesting the catheter tip is not optimally located, but often precluding replacement using electrical current.

Alternatively, catheters which deliver current to their tips have been developed in an attempt to improve initial placement success rates.[14] These catheters provide feedback on the positional relationship of the catheter tip to the target nerve prior to local anesthetic dosing. There is data to suggest that in the area of the popliteal fossa, using stimulation during catheter advancement results in the catheter tip being placed closer to sciatic nerve.[15-18] The clinical relevance is questionable femoral and interscalene catheters. [19-27] Regrettably, stimulating catheters guarantee neither a complete surgical block nor an effective postoperative infusion.[21,28-30] Furthermore, an acceptable muscle contraction may not always be obtained during catheter insertion;[21,31-34] and, stimulating catheters often require an increased insertion time and cost more than their non-stimulating counterparts,[18] resulting in many questioning their cost-benefit ratio. Finally, the minimal acceptable current resulting in a muscle contraction remains unknown.

Also remaining unknown is the optimal distance to insert the catheter past the needle tip. However, increasing the insertion distance is correlated with an increased the risk of catheter coiling, and perhaps the ultimate distance between the catheter and target nerve.[35] With catheter insertion over 5 cm, numerous catheter knots have been reported;[36] and, a maximum insertion of 5 cm appears warranted. Likewise, remaining unknown is the optimal minimum insertion distance; but, studies suggests that 0-1 cm results in a minimal risk of secondary block failure,[6] but possibly an increased risk of subsequent dislodgement.

Catheter Insertion (Ultrasound). The limited length of this article precludes an in-depth discussion of ultrasound-guided perineural catheter insertion; but, the information is available elsewhere.[37] While ultrasound guidance would intuitively seem to increase the accuracy of catheter tip location, identifying the catheter tip is often challenging. Multiple practitioners observe the location of injected fluid,[38] an agitated fluid/air mixture,[39] or simply air.[40,41] For most anatomic locations, ultrasound-guided insertion decreases insertion time and associated discomfort compared with an electrical technique (and provide at least similar analgesia). [31,32,34,42-45] The majority of reports of combining ultrasound and nerve stimulation suggest little benefit,[39,46-50] Currently, insufficient data are available to determine either the optimal techniques/equipment for these insertion modalities, as well as their associated risks and benefits.[37]

Infusates. The majority of perineural infusion publications have involved bupivacaine or ropivacaine, although levobupivacaine and shorter acting agents have been reported. While the available data suggests bupivacaine and levobupivacaine are more potent than ropivacaine,[51] all three provide similar analgesia within human trials, although the ropivacaine concentration is often increased up to 50% to compensate for decreased potency.[51,52] When a bupivacaine perineural infusion is paused, the motor and sensory effects greatly outlast those of ropivacaine.[52] This is often important when titrating dose to limit undesired CPNB effects. Also unknown is whether the primary determinant of CPNB effects is only local anesthetic dose/mass, or if volume (rate) and/or concentration have an influence.[53-55] Currently, additional research is warranted, and no optimal concentration/rate combination may be recommended for all anatomic locations.[56] For bupivacaine/levobupivacaine and ropivacaine, the most-commonly-cited concentrations are between 0.1-0.125% and 0.1-0.2%, respectively. Unfortunately, no adjuvants—such as clonidine, epinephrine, and opioids—have been found to improve analgesia and/or decrease undesirable CPNB-related side effects; and infusing solely long-acting local anesthetic appears warranted.

Local Anesthetic Delivery Regimens. Currently available data suggest that following procedures producing moderate-to-severe pain, providing patients with the ability to self-administer local anesthetic doses increases perioperative benefits and/or decreases local anesthetic consumption. Unfortunately, insufficient information is available to base recommendations on the optimal basal rate, bolus volume, or lockout period accounting for the many variables that my effect these values (e.g. catheter type, location, surgical procedure). Until recommendations based on prospectively-collected data are published, practitioners should be aware that investigators have reported successful analgesia using the following with ropivacaine (0.2%) or bupivacaine (0.125%): a basal rate of 5 (lower extremity) or 8 (upper extremity) mL/h; a bolus volume of 2 – 5 mL; and a lockout duration of 20 – 60 min. Additionally, the maximum safe dose remains unknown. However, multiple investigations involving patients free of renal or hepatic disease have reported blood concentrations within acceptable limits—and an absence of toxicity symptoms/signs—following multiple weeks of perineural infusion with similar dosing schedules.[57,58]

Infusion Pumps. There is no single optimal infusion pump for every clinical scenario; and, therefore, pump preference is usually dictated by desired device characteristics.[59] Although elastomeric infusion pumps cannot match their electronic counterparts in delivering a basal infusion rate within ±5% expected for the entire infusion duration, whether the increased variability is clinical significant—or in which clinical situations it is relevant—remains unknown.[59] Providing an adjustable basal infusion rate permits titration of local anesthetic dose for inadequate analgesia, an insensate extremity, undesired side effects (e.g., muscle weakness),[60] or maximizing infusion duration (e.g., ambulatory patients with a set reservoir volume). Furthermore, multiple clinical benefits are provided with a patient-controlled bolus option, such as increasing analgesia and decreasing opioid consumption. Electronic pumps provide an adjustable basal rate, patient-controlled bolus doses, and a variable bolus lock-out period.[59] And, while most elastomeric devices include a fixed basal infusion rate, a few provide similar flexibility to electronic pumps.

Elastomeric pumps are often preferred for their smaller size and lighter weight; lack of audible alarms; disposability; and silent operation (electronic pumps may disturb patient sleep). In addition, elastomeric devices with no bolus dose capability and a manufacturer-fixed basal rate are usually less costly. However, inexpensive disposable "cassettes" provide sterile infusion for individual patients utilizing reusable electronic pumps. A few disposable electronic pumps are available. At least within the United States, the infusion pump/reservoir must now be filled under a laminar flow workbench.[61] Of note, at least within the United States, there are no national guidelines regarding the maximum safe CPNB duration.[61]

Ambulatory Perineural Infusion. While length limitations of this article preclude an extensive discussion of ambulatory CPNB, this information is available elsewhere.[59] Ambulatory perineural infusion may be provided to outpatients using a portable pump. Perineural infusion is often provided for ambulatory surgery without an overnight hospital stay;[59] but may also shorten hospitalization duration,[62,63] and/or bestow benefits following discharge to either a rehabilitation facility or home.[6,58] Ultrasound guidance—with its demonstrated decreased insertion time—is often beneficial in high-turnover ambulatory centers where time constraints are often severe.[31,34,45,64] Patient selection criteria are often more stringent for ambulatory CPNB since outpatients are rarely directly monitored; and not all patients desire or are capable of accepting the additional responsibility of caring for the catheter and pump system. Patients with hepatic or renal insufficiency are often excluded from ambulatory CPNB to decrease the risk of local anesthetic toxicity. Caution is warranted during interscalene and cervical paravertebral infusion (frequently induce diaphragm weakness) for obese individuals and those with heart/lung disease who may not be able to compensate for mild hypoxia and/or hypercarbia.

Ambulatory perineural infusion may reduced time until discharge *readiness*;[6,29,62,65] and, in select cases, *actual* discharge.[62,63] Early discharge after total knee arthroplasty may decrease hospitalization-related costs.[66] However, caution is warranted prior to allowing discharge with a continuous posterior lumbar plexus and femoral nerve block given that these catheters are associated with an increased risk of falling.[67] Nonetheless, relatively small published series document the feasibility of total joint arthroplasty with only a single-night hospital stay—or even on an outpatient basis—when patients are provided CPNB at home.[68-72]

Benefits. The most-common indication for CPNB is to provide postoperative pain control, and it appears that most CPNB benefits are dependent upon successfully improving analgesia.[56] RCT-documented benefits include decreased postoperative pain, supplemental analgesic requirements, opioid-related side effects, sleep disturbances, dissatisfaction, discharge readiness, actual discharge, and inflammatory markers. In addition, an accelerated resumption of passive joint range-of-motion is documented following total knee arthroplasty procedures with 48-72 hours of continuous femoral perineural infusion. Analgesia is most impressive when the perineural infusion effects the entire innervation of the surgical site; as is often the case for shoulder and foot procedures (interscalene and sciatic perineural catheters, respectively).[4,7,62] Unfortunately, even though brachial plexus infusions (theoretically) cover the entire surgical site for procedures at or distal to the elbow, they provide less impressive analgesia.[73]. Severely lacking are RCT-documented benefits of continuous axillary,[74] supraclavicular,[75] and transversus abdominus plane blocks.[56] And, while the benefits of infraclavicular infusion are validated,[73] analgesia is often less-than-optimal unless a high enough dose of local anesthetic is administered, frequently rendering the extremity insensate. Similarly, for surgical sites innervated by multiple nerves (such as the knee, hip and ankle), a single perineural usually provide less-than-optimal analgesia without the concurrent use of additional analgesics.[6,29,55] While a lumbar epidural provides roughly equivalent analgesia to femoral perineural infusion for hip and knee arthroplasty, CPNB results in a more-favorable side-effect profile without the risk of epidural hematoma during concomitant anticoagulant administration.[76-78]

While the evidence for CPNB benefits *during* the infusion is vast,[56] there are few studies documenting benefits *following* catheter removal. Exceptions include increased health-related quality-of-life in one study[79] (but not five others);[80-84] improved analgesia after a few days[5,85,86] or six months;[87] faster tolerance of passive knee flexion resulting in earlier discharge from rehabilitation centers;[77,78,85] and more-rapid resumption of lavatory use and unassisted standing.[85] Noticeably absent is evidence of medium- or long-term improvements in measures of health-related quality-of-life.[80-84,88] See below for additional information.

Complications. Relatively minor CPNB-related complications occur at a frequency similar to single-injection peripheral nerve blocks.[89] In contrast, severe and permanent infusion-related injuries are uncommon. Unfortunately, generalizations are difficult given the multiple anatomic locations for perineural infusion as well as diverse equipment and techniques. For example, the incidence of secondary block (infusion) failure reported by three different trials includes 1%,[90] 20%,[7] and 50%.[9] Catheter insertion-related complications include inaccurate catheter tip placement; and—in extremely rare cases—intraneural, intrathecal, epidural, intravascular, and even interpleural catheter insertion. Complications during the perineural infusion include catheter obstruction or dislodgement; catheter site fluid leakage; infusion pump disconnection, malfunction, or undesired pause; allergic reaction or simply skin irritation to the catheter dressing and/or liquid adhesive; and, catheter-induced brachial plexus irritation. One of the most common complications is an insensate extremity that may be unnerving to patients, hinders rehabilitation, and often believed to be a risk factor for injury.[54,55] In such cases, pause the infusion until sensory perception returns, and then restarted the infusion at a lower basal rate. Conversely, breakthrough pain or persistent inadequate analgesia may be treated with patient-controlled bolus doses and increasing the basal infusion, respectively.

More serious—and remarkably uncommon—complications include systemic local anesthetic toxicity; myonecrosis with repeated large boluses of bupivacaine; retroperitoneal and peri-catheter hematoma formation; catheter knotting, retention, shearing, or breakage; a prolonged Horner's syndrome; and lower lobe collapse during infusions affecting the phrenic nerve. In patients with preexisting neuropathy and/or diabetes, limited evidence suggests that prolonged local anesthetic exposure may increase the risk of nerve injury. Infusions affecting the femoral nerve is associated with an increased risk of falling following knee and hip arthroplasty.[67] Catheter site infection and abscess are rare (infection incidence 0-3%;[91,92] but most reports <1%),[11,89,93] although inflammation (3-4%)[1,90,94] and bacterial colonization (6%-57%) are more common. Risk factors include the absence of perioperative antibiotic prophylaxis, male sex, axillary/femoral catheter insertion, and presence in an intensive care unit.[1] The infection risk is also correlated with infusion duration;[1] but, nevertheless, a minimal incidence of infection has been reported for CPNB during inter-continental transportation for up to 34 days[95] and provided at home for up to 83 days.[58]

Because all surgical procedures are associated with a variable incidence of nerve injury—regardless of the application of a regional anesthetic/analgesic—it is often problematic to determine what percentage (if any) of a new-onset neurologic deficit is attributable to CPNB. Keeping this limitation in mind, the incidence of *transient* adverse neurologic symptoms *associated* with CPNB is 0-1.4% for interscalene,[1,11,89,90] 0.4-0.5% for femoral,[1,96] and 0-1.0% for sciatic catheters.[1,90,96,97] Another study reported a 0.2% incidence of neurologic deficits lasting longer than 6 weeks in nearly 3,500 catheters from multiple anatomic locations.[90] In this latter study, it remains unknown if the deficits resolved after the 6-week study period; but multiple prospective investigations report that the overwhelming majority of neurologic symptoms present at 4-6 weeks resolve spontaneously within three months of surgery.[1,11,89] *Long-term* and/or *permanent* nerve injury has occurred.[98] Five large,[1,11,89,96,97] prospective series that followed patients for at least three months reported 3 cases of unresolved adverse neurologic events.[89,96,97] These investigations combined (4,148 total subjects) suggests the risk of neurologic injury lasting longer than nine months *associated* with CPNB is 0.07% (all of the risk may not be conclusively attributed to the perineural infusion).[1,11,89,96,97] While ultrasound-guidance may decrease the incidence of many/most of these reported complications,[99] to date there are few data supporting this proposition;[100,101] and case reports suggest that completely abolishing such events is unlikely.[102-104]

There has been a significant amount of data published in the last few years involving neurologic risk in the presence of a CPNB.[105] In most cases of postoperative neurologic symptoms, it is problematic assigning causality to the surgical procedure, CPNB, or simply general anesthetic (e.g., positioning injuries on an unrelated part of the body). Interpreting the available data is further complicated due to a lack of controls and/or randomization, which lead to multiple types of bias. An excellent example is a prospective, uncontrolled cohort study of patients with continuous popliteal-sciatic nerve blocks (n=151) following foot and ankle surgery reporting an alarming 41% incidence of

postoperative neurologic symptoms (PONS) within 2 weeks, 24% at 34 weeks, and 4% following 48 weeks.[106] A similar retrospective study (n=157) found a 1.9% incidence of unresolved PONS at 11 months.[107] These risks are an order of magnitude higher than previous estimates for popliteal infusions (0-0.4%),[108,109] and are most-likely due to numerous biases, beginning with selection bias.

Another relatively new retrospective investigation of 1,182 continuous interscalene and femoral nerve blocks identified 4 (0.3%) patients with PONS at any time point, with one of these cases resolving by 6 months.[110] Of note, these investigators reported an increased incidence of PONS lasting more than 6 months among patients with continuous versus single-injection peripheral nerve blocks (0.24% vs. 0.07%, P=0.08).[110] It is important to be aware of the very high risk of selection bias from this retrospective, nonrandomized cohort (e.g., larger surgical procedures—with inherently higher neurologic risk—more represented in the catheter group). The most reliable, recently-published data is derived from two *prospective* investigations of over 2500 interscalene and femoral catheters, reporting a PONS incidence of 4.9-5.3% resolving by 6 months, with all but 0.3-0.7% of these resolving by 11 months.[111,112] To emphasize, it is critical that practitioners are cognizant of the fact that these values approximate association and not necessarily causation: an unknown percentage of subjects with PONS would have experienced them without any regional analgesic due to the surgery or other factors. Unfortunately, the available data does not suggests that ultrasound guidance has a "meaningful impact on the incidence of PONS," so switching from a different insertion technique is not expected to decrease the rate of PONS.[113]

The risk of falling following knee and hip arthroplasty have become better appreciated within the previous decade.[114,115] Single-injection femoral nerve blocks do not appear to increase this risk;[116] but data from randomized, controlled trials suggest that a continuous femoral or psoas compartment block is associated with a 4-5 time increased risk of falling,[117-119] although some investigators have questioned this correlation.[120,121] Regardless of the relationship between CPNB and falls, this complication continues to occur even with the implementation of specific, intensive fall-prevention programs.[122-125] While replacing continuous femoral nerve blocks with adductor canal infusions have been proposed as a method to decrease the risk of falling due to decreases induced quadriceps weakness,[126,127] such an association has yet to be demonstrated.[127,128]

Benefits (Update). Novel indications for CPNB have been published within the past few years, suggesting benefits for an even wider array of morbidities.[129-150] New RCTs have provided evidence that adding a perineural infusion following a single-injection peripheral nerve block improves postoperative analgesia (and in most cases decreases supplemental analgesic requirements) using interscalene,[151-153] paravertebral,[154] adductor canal,[143-148] femoral,[155-158] and sciatic catheters (Table 3).[159-162] Compared with epidural infusions,[163] CPNB provides similar analgesia[164] but improves hemodynamic stability (presumably by inducing less sympathectomy),[165-167] and following knee arthroplasty shortens the time to achieve flexion goals, improves analgesia, and lowers supplemental analgesic requirements.[157] Compared with intrathecal morphine, continuous posterior lumbar plexus blocks provide similar analgesia with lower supplemental opioid requirements and incidence of pruritis.[168] And, data continues to accumulate demonstrating that CPNB provides superior analgesia compared with continuous wound infusions.[169,170]

Due to the association between continuous femoral nerve blocks and falling after knee arthroplasty,[117,118,125] the last five years have seen a plethora of research validating adductor canal catheter effectiveness following major knee surgery,[143-148] based on the theory that any risk of falling will be decreased due to less induced quadriceps weakness compared with femoral infusion (Table 3).[126,127] Of the 6 RCTs directly comparing continuous adductor canal and femoral nerve blocks,[126,127,171-174] 3 demonstrated dramatic improvements for subjects with adductor catheters in the ability to stand, sit, ambulate, and climb stairs.[126,171-173] One study did not investigate ambulation;[174] but, the 2 remaining RCTs failed to detect mobilization improvements using an adductor infusion—although they did document and quantify improved quadriceps femoris strength (52% vs. 18% of baseline in one).[126,127] It is noteworthy that these two latter studies provided solely a fixed basal infusion (8 mL/h) without either patient-controlled or repeated provider-administered bolus doses,[126,127] which may have decreased adductor infusion effectiveness. In addition, two of the RCTs detected improved analgesia for subjects with femoral infusions at either rest (unicompartment arthroplasty)[173] or with movement (tricompartment arthroplasty),[172] while the others failed to detect differences between the two catheter locations. Lastly, one of the investigations reported a decreased time until discharge favoring the adductor catheters (3.1 vs. 3.9 days),[171] although there were issues raised regarding its protocol/findings[175-177] and a similar RCT detected no decrease in time until discharge readiness or actual discharge,[172] albeit with slightly different criteria. What does appear likely is that continuous adductor canal blocks

are associated with greater mobilization ability while providing at least similar analgesia compared with their femoral counterparts.[178] What remains unclear is the ideal catheter insertion location/protocol,[179,180] optimal method of local anesthetic delivery (e.g., basal infusion vs. repeated bolus doses, basal rate, bolus volume, etc.) and if an optimized delivery regimen can shorten hospitalization duration.[181-183]

In an effort to further improve analgesia following total knee arthroplasty,[184,185] three recent RCTs have investigated the effects of adding a continuous sciatic nerve block to a continuous femoral or posterior lumbar plexus (psoas compartment) block.[160-162] All demonstrated lower pain scores and decreased supplemental analgesic consumption,[160-162] and one detected a lower incidence of nausea and vomiting as well as improved knee flexion and ambulation.[161] As has been previously opined, there are potential drawbacks to providing a continuous sciatic nerve block such as the extra time required to place a second catheter, an inability to fully evaluate sciatic nerve function postoperatively,[186] and interference with physical therapy goals (e.g., foot drop, leg weakness).[187]

While there are relatively few demonstrated benefits of CPNB following catheter removal,[188] there are significant additions to our knowledge base within recently-published data. Two RCTs found that a 2-3 day postoperative continuous interscalene or femoral nerve block resulted in less pain,[152,189] opioid requirements,[152,189] and sleep disturbances[152] on postoperative day 7 compared with a control group following shoulder and knee procedures, respectively. Similarly, two RCTs add to the previous evidence that a continuous femoral nerve block following total knee arthroplasty improves joint flexion for up to 6 months.[157,189]

However, it is the possibility of decreasing persistent post-surgical pain that has perhaps garnered the most attention and optimism.[190,191] Four new RCTs add data to the single previous positive study that involved the addition of a femoral catheter to a popliteal infusion for major ankle surgery.[192] One study reported that providing a continuous femoral nerve block following total knee arthroplasty reduced chronic pain at 3 and 6 months;[189] and, another involving the same surgical procedure found that providing a continuous sciatic nerve block in addition to a femoral infusion resulted in a reduction of dynamic pain at 3 months (no difference at 12 months for either trial).[193] Finally, two RCTs investigating continuous paravertebral blocks following mastectomy detected improvements in analgesia up to a full year following surgery,[194,195] including superior physical and mental health-related quality-of-life[194] and decreased pain-related physical and emotional dysfunction.[195]

Liposome Bupivacaine

Liposomes consist of two hydrophobic tails and a hydrophilic head,[196] and can form vesicles to act as a medication "depot" (Figure 1).[197,198] Following administration, the liposomes gradually break down, resulting in an extended release of medication.[199,200] Combining liposomes and a local anesthetic (lidocaine) was first proposed in 1979,[201] initially used in humans in 1988,[202] and first reported for postoperative analgesia in 1994.[201,203] Although multiple subsequent reports were published,[204-212] a liposome local anesthetic was not approved by the United States FDA until 2011 (Exparel liposome bupivacaine, Pacira Pharmaceuticals, Parsippany, New Jersey) for administration at the surgical site to provide postoperative analgesia in adults.[198]

Two multicenter RCTs demonstrated superior postoperative analgesia of this approved medication compared with placebo wound infiltration following hemorrhoidectomy[213] and bunionectomy.[214] In contrast, when compared with bupivacaine HCl ("standard" bupivacaine), 10 of the 12 currently-published RCTs were negative for their primary (and most secondary) analgesic end points.[215-221] Of the two positive RCTs versus bupivacaine HCl, one involved hemorrhoidectomy,[222] although another similar trial had negative results.[215] The second positive RCT involved submuscular augmentation mammoplasty in which mean pain scores were reduced by less than 1 on the 0-10 numeric rating scale and the investigators concluded, "…it is our assertion that the additional cost of liposomal bupivacaine is unjustified for this particular use."[223] Some of these 14 RCTs were dose-response studies, not powered to be a conclusive test of efficacy; and, when combined with the placebo-controlled trials, there were some detected positive associations for secondary end points such as pain scores at individual time points,[224] opioid use (although differences were minimal),[224] and duration until first use of opioid analgesics.[215,224] However, considering the new medication costs an estimated 100 times that of bupivacaine HCl, it is incumbent upon those proposing the conversion to produce data conclusively demonstrating superiority.[221] Various large RCTs currently ongoing should provide much-needed data to help practitioners make evidence-based decisions involving this analgesic modality (ClinicalTrials.gov NCT02713490, NCT02111746, NCT02197273).

There are no RCTs directly comparing CPNB with liposome bupivacaine wound infiltration.[225] The only direct comparison to a single-injection femoral nerve block following total knee arthroplasty suggests that liposome bupivacaine infiltration provides inferior analgesia during the duration of the peripheral nerve block without subsequent differences between the two treatments.[226] Considering there are now four negative published RCTs comparing liposome bupivacaine with bupivacaine HCl following total knee arthroplasty,[215,217-219] and the literature is replete with positive studies involving CPNB,[188] the evidence certainly does not suggest even equivalence between these two modalities.

In contrast to wound infiltration, recently-published data from one RCT strongly suggests that liposome bupivacaine within a single-injection subcostal TAP block provides statistically and clinically superior analgesia to bupivacaine HCl up to 3 days following robotic assisted hysterectomy.[227] In a separate RCT, few differences were detected between a continuous subcostal TAP block and epidural infusion following open renal or hepatobiliary surgery,[142] although this investigation was designed as a superiority study and the negative findings should be viewed as inconclusive and not equivalence. Therefore, a randomized comparison of a TAP with liposome bupivacaine bolus compared with either a epidural infusion or perineural local anesthetic TAP infusion appears warranted.[228,229] Of note, the United States FDA recently revised the label for the single approved liposome bupivacaine formulation explicitly including, "infiltration into the transversus abdominis plane (TAP) which is a field block technique [is] covered by the approved indication for EXPAREL."

Although no liposome local anesthetic is currently approved for use within the epidural space[230] or peripheral nerve blocks, a great deal of related research has been completed (if not all published).[198] Both preclinical toxicology and clinical data indicate that liposome bupivacaine has at least as favorable safety profile as bupivacaine HCl.[231-241] Though phase 1-3 clinical trials involving the use of liposome bupivacaine have been reported for intercostal and ankle blocks,[197,198,231] the most published data may be found for femoral nerve blocks.[242,243] No direct comparisons with CPNB are available, but liposome bupivacaine in a femoral nerve block produced over 72 hours of analgesia with an incomplete motor block in healthy volunteers,[242] and demonstrated analgesic activity for up to 72 hours versus placebo in subjects following total knee arthroplasty (albeit extraordinarily minimal analgesic differences following 24 hours).[243] Further sizable RCTs involving adductor canal, brachial plexus, and femoral nerve blocks with liposome bupivacaine are ongoing (ClinicalTrials.gov NCT02607579, NCT02713230, NCT02713178).

Theoretical benefits over CPNB include the avoidance of catheter insertion (e.g. less procedure time, no catheter management/removal), the lack of an infusion pump and anesthetic reservoir to purchase/carry, a lower risk of infection, and no risk of catheter dislodgement or leakage. It is emphasized that at the time of this writing, there are no liposome bupivacaine local anesthetics approved for use in the epidural space[230] or peripheral nerve blocks (other than the possible exception of TAP blocks, depending on how this block is categorized).

Cryoneurolysis (Cryoanalgesia)

Cryoneurolysis is the application of exceptionally low temperatures to reversibly ablate peripheral nerves, resulting in temporary analgesia termed "cryoanalgesia".[244] The first cryosurgical apparatus was described in 1961,[245] and modern cryo probes transmit a gas (usually nitrous oxide or carbon dioxide) at high pressure down their length, through a minute opening, and into the sealed distal tip at a lower pressure (Figure 2a).[246] Due to the Joule-Thompson effect, a large drop in temperature occurs when the gas moves from a high to low pressure inducing brisk expansion and absorption of heat.[247] The gas is returned out of the body through a larger-diameter (low pressure) cylinder in the middle of the shaft. This closed circuit ensures that all gas exits the body. The intense cold temperature at the probe tip produces Wallerian degeneration—a reversible breakdown of the nerve axon—subsequently inhibiting transmission of afferent and efferent signals. However, because the temperature resulting in irreversible degeneration—about -100°C—is colder than the boiling point of the gas (carbon dioxide: -79°C; nitrous oxide: -88°C), the remaining endoneurium, perineurium, and epineurium remain intact and the axon regenerates at a rate of approximately 1-2 mm/day.[246]

Cryoneurolysis has been used *via* the surgical incision to treat acute pain following thoracotomy,[248-264] tonsillectomy,[265] and herniorrhaphy.[266,267] Alternatively, ultrasound may be used to guide[268,269] a percutaneously-inserted probe to a peripheral nerve to provide analgesia, and has been described for various chronic pain conditions.[270-275] The combination of ultrasound and newly-designed, FDA-approved hand-held cryoneurolysis devices[276,277] may now make percutaneous cryoanalgesia a valuable postoperative analgesic alternative to CPNB

(Figure 2b).[244] The largest limiting factors when applying this technique to acute pain states are (1) the inhibition of efferent signals effectively paralyzing innervated muscles; and, (2) the relatively unpredictable duration of action measured in multiple weeks, and often months. Therefore, the modality has historically been used to target sensory-only nerves,[278] although mixed motor-sensory nerves have been cryoablated to treat spasticity[279] and preclinical studies found no lasting changes to the structure or function of motor nerves following remyelination.[276,277]

Surgical procedures possibly amenable to cryoneurolysis include iliac crest bone harvesting (superficial superior cluneal nerves), total knee arthroplasty (anterior femoral cutaneous and infrapatellar saphenous nerves), various thumb surgeries (superficial branch of the radial nerve), rotator cuff repair (suprascapular nerve), and digit/limb amputations, among others.[244,246] Although there are available cryoneurolysis devices currently approved by the United States FDA for relief of pain, the use of cryoanalgesia to treat acute pain requires a great deal of further investigation with both RCTs and large series. It remains undetermined whether the duration of denervation can be shortened (e.g. decreasing the freezing interval or number of cycles); and, the incidence of adverse events such as neuralgias following thoracotomy.[262-264] Direct comparisons with CPNB are unavailable, but some theoretical benefits of cryoneurolysis include an ultra-long duration of action, no catheter management/removal, the lack of an infusion pump and anesthetic reservoir to carry, a lower risk of infection, and no risk of local anesthetic toxicity, catheter dislodgement or leakage.

Percutaneous Peripheral Nerve Stimulation

Electric current applied in both the central and peripheral nervous systems induces analgesia. There are numerous theories regarding the mechanism of action,[280] but most are usually based on Melzack and Wall's "gate control theory":[281] current activates large-diameter myelinated afferent peripheral nerves which then—within the spinal cord— impede pain signal transmission from small-diameter pain fibers to the central nervous system.[282,283] Implanted spinal cord and peripheral nerve stimulators have since been used to treat multiple chronic pain states.[284-288] In contrast, the use of peripheral nerve stimulation to treat acute/postoperative pain is extraordinarily rare,[289-291] in no small part due to cutaneous pain fiber activation with transcutaneous electrical nerve stimulation[282] and the invasive requirement of surgically implanting/removing peripheral nerve electrodes/leads.[292,293]

Electrical leads are now available with a diameter small enough to allow passage through a needle, allowing percutaneous insertion (Figure 3a).[294-296] Perineural placement is possible using ultrasound guidance,[297,298] and has been reported to treat chronic pain.[299-302] More recently, postoperative pain was treated using ultrasound-guided percutaneous peripheral nerve stimulation.[303] Femoral—and in 2 cases sciatic—leads were inserted in subjects (n=5) 8-58 days following total knee arthroplasty.[303] Percutaneous peripheral nerve stimulation decreased pain an average of 93% at rest (reduced from a mean of 5.0 to 0.2 on a 0-10 numeric rating scale), with 4 of 5 subjects experiencing complete resolution of pain. During passive and active knee motion pain decreased an average of 27% and 30%, respectively. Neither maximum passive nor active knee range-of-motion was consistently affected in this small cohort of subjects.

There are no direct comparisons with CPNB, but theoretical benefits of percutaneous peripheral nerve stimulation are numerous.[303] Leads function optimally when inserted 0.5-3.0 cm from a target peripheral nerve, negating the importance of location within a particular facial plane. Electrical generators are now so minute that their footprint is smaller than a business card and may be literally adhered to a patient's limb—so, there is no large portable infusion pump or local anesthetic reservoir to carry (Figure 3b). Helically coiled leads are designed to minimize the risks of migration and fracture, and decrease the infection risk to approximately 0.05 per 1000 indwelling days.[303] These characteristics permit a dramatically-long duration of lead retention—well-over a year in some cases[304-306]—raising the possibility of preoperative insertion and continued postoperative stimulation for the entire interval of surgically-related pain.[304-308] There are theoretically no induced sensory, proprioception, or motor deficits, enabling full engagement in physical therapy and likely lacking any association with an increased falling risk. Obviously, there is no risk of local anesthetic toxicity or leakage. Conversely, practical implementation of percutaneous peripheral nerve stimulation to treat acute pain states is dependent upon multiple factors that are currently undetermined: the time required for lead insertion, the cost of leads and electrical generators, the maximum provided analgesia, and the future availability of a United States FDA-approved lead and generator.[309]

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Anesthetic Management of the Severely Preeclamptic Patient

Joy L. Hawkins, M.D. **Aurora, Colorado**

Introduction

Hypertensive disorders of pregnancy are responsible for 11% of maternal deaths after a live birth in the U.S, usually from a cerebrovascular accident.[1] Preeclampsia occurs in 6-8% of pregnancies; 75% of cases are mild and 25% are classified as severe. Anesthesiologists ***will*** be involved when high risk parturients deliver, and we must be a respected team member caring for these critically ill women.

Definitions

The American Congress of Obstetricians and Gynecologists (ACOG) classification system for hypertensive diseases of pregnancy clarifies terminology and provides an estimate of risk for the mother and fetus.[2]

- Preeclampsia / Eclampsia presents after 20 weeks' gestation with hypertension > 140/90, proteinuria, and a spectrum of multi-organ system dysfunction such as thrombocytopenia. HELLP syndrome is a subset of severe preeclampsia defined by hemolysis (H), elevated liver enzymes (EL) and low platelets (LP).
- Chronic hypertension is unrelated to pregnancy, presenting before 20 weeks' gestation or before conception.
- Preeclampsia superimposed on chronic hypertension presents with worsening or difficult-to-control hypertension, new onset thrombocytopenia, or other systemic manifestations of preeclampsia. This diagnosis carries substantial increased risk for the mother and fetus.
- Transient or gestational hypertension is hypertension in late pregnancy, without other evidence of preeclampsia that completely resolves postpartum. There is minimal risk to the mother or her fetus, although ACOG now recommends delivery at 37 weeks.
- The terms "PIH" or "pregnancy-induced hypertension" are no longer used.

Etiology and Pathogenesis

Despite decades of research, the etiology of preeclampsia remains unknown. Preeclampsia is a syndrome that 1) only occurs in pregnancy, 2) is characterized by maternal inflammation, and 3) is associated with the presence of a placenta.[3] Theories include placental ischemia, an immunologic origin, and genetic predisposition. No theory has withstood the test of time, and no preventive measure has proven useful.

Preeclampsia is not yet preventable. Early diagnosis and appropriate management may prevent maternal sequelae such as seizures or organ failure. However, early delivery is the only effective treatment and unfortunately often necessitates preterm birth. Preventive measures that have been tested include supplementation with magnesium, zinc, fish oil, anti-oxidant vitamins (C and E) and calcium, protein or salt restriction, antihypertensive medications in women with chronic hypertension, and exercise.[4] None have reduced the incidence of preeclampsia. Low-dose "baby" aspirin therapy however *does* reduce the occurrence of preeclampsia in high-risk pregnancies. New guidelines from the U.S. Preventive Services Task Force state that women at increased risk of preeclampsia (e.g. preeclampsia in a previous pregnancy) derive more benefit than harm from taking low-dose aspirin.[5] They found no maternal or newborn risks. USPSTF recommends 50-160 mg/day from 12 until 28 weeks' gestation. A cost analysis found that administering 81 mg aspirin to all pregnant women would also be cost effective based on savings for fewer preterm births and less maternal complications related to preeclampsia.[6] Another promising pilot study randomized women at high risk of preeclampsia to placebo or pravastatin 10 mg daily when they were 12-16 weeks gestation.[7] There were no identifiable safety risks to mother or baby. In the placebo group, 25% of women developed preeclampsia versus none in the pravastatin group. Statin therapy merits further study based on risk-benefit analysis.

Although the etiology of preeclampsia remains elusive, the risk factors for developing preeclampsia are well known. The strongest contemporary risk factor is obesity, with a dose-response risk such that BMI > 40 has an odds ratio (OR) of 6 for developing preeclampsia.[8] Other significant risk factors include diabetes (OR 3.9), multiple gestation (OR 3), chronic hypertension (OR 2.7), African-American race (OR 1.9), nulliparity (OR 1.7), and infertility techniques (OR 1.7).[8]

The pathophysiology of preeclampsia is different in early and late stages. The early stage involves abnormal placentation. The spiral arteries fail to become the dilated, flaccid vessels seen in normal pregnancies, and may even show signs of atherosis. The placenta becomes ischemic and releases vasoactive substances. Maternal hemodynamics are hyperdynamic with elevated cardiac output. Later in gestation, the disease manifests as a

maternal systemic disorder with increased vascular sensitivity to any pressor agent, activation of the coagulation cascade, microthrombi and intravascular fluid loss. Vasospasm, hemoconcentration, and ischemic changes in the placenta, kidney, liver and brain are seen. Maternal hemodynamics show elevated SVR and reduced cardiac output.

Prediction and Diagnostic Tools

A gene encoding protein sFlt1 is overactive in preeclamptic placentas. sFlt1 is known to thwart blood vessel growth; i.e., it is anti-angiogenic. There is growing evidence that measuring elevated antiangiogenic proteins such as soluble Flt1 and soluble endoglin can predict preeclampsia months before its clinical onset.[9] These proteins are secreted by the placenta and increase in the maternal circulation weeks before the onset of preeclampsia, producing systemic endothelial dysfunction such as hypertension, proteinuria and other manifestations of preeclampsia. A systematic review of the literature on use of elevated sFlt-1 and reduced placental growth factor (PlGF – a pro-angiogenic protein) to predict preeclampsia concluded that third-trimester increases in sFlt-1 combined with decreases in placental growth factor levels are associated with severe preeclampsia. Measuring soluble sFlt-1 and soluble endoglin levels in gestational hypertension, chronic hypertension, preeclampsia and normal pregnancies demonstrated a high sensitivity and specificity in differentiating women with preeclampsia from those with other hypertensive diseases during pregnancy.[9] Women presenting with hypertension after 20 weeks gestation are often admitted and monitored to rule out preeclampsia, leading to increased costs. Could a blood test help clinicians decide who could be followed safely as an outpatient? A study examined 550 women with suspected preeclampsia between 24 and 37 weeks who had their sFlt-1 and placental growth factor measured.[10] If the ratio was < 38 there was a 99.3% chance she would not progress to preeclampsia or HELLP within the next week.

Controversial Areas in the Clinical Management of the Patient with Preeclampsia

- When and by what route should delivery occur, especially when preeclampsia develops early in the 3rd trimester and the preterm newborn's morbidity will be high?
- When should invasive monitoring be used to optimize care of the mother? Is there a place for non-invasive monitoring techniques?
- What are the benefits and risks of various anti-hypertensive medications? What does ACOG recommend?
- How should we manage an eclamptic seizure?
- Why administer magnesium sulfate rather than other anti-seizure medications?
- What is optimal fluid management?
- Platelet counts – how low can we go and still safely administer neuraxial anesthesia?
- Is spinal anesthesia for cesarean delivery safe and appropriate in severe preeclampsia?
- Should α-agonists (e.g. phenylephrine) replace ephedrine as our first-line pressor to treat hypotension after neuraxial techniques?

Current Obstetric Management Strategies

The only cure for preeclampsia is delivery, but the benefit to the mother must be weighed against the risks to the fetus of prematurity. Women with gestational hypertension or mild preeclampsia may be managed expectantly at home with frequent maternal monitoring and fetal surveillance. Patients with severe preeclampsia must be admitted to L&D for continuous maternal and fetal assessment and development of a delivery plan. Those with a favorable cervical exam should undergo induction of labor because neonates delivered vaginally have a lower incidence of RDS. Elective cesarean delivery may be preferable in very preterm pregnancies if the cervical exam is unfavorable.

Maternal assessment must define the extent of end-organ involvement. Systems evaluated should include: hematologic (↓ platelets, hemolysis), hepatic (epigastric pain, ↑ LFT), neurologic (headache, visual changes), renal (oliguria, proteinuria, ↑ creatinine), pulmonary (pulmonary edema), and the placenta (growth restricted fetus, oligohydramnios, abnormal umbilical artery Doppler studies). Fetal evaluation will include a non-stress test, ultrasound for amniotic fluid volume, fetal growth percentile, estimate of gestational age, and a biophysical profile. Based on these results, a decision for immediate delivery versus in-hospital expectant management will be made. If the pregnancy is < 34 weeks, the obstetrician may delay delivery for 48 hours to administer steroids for fetal lung maturity, but this requires daily maternal and fetal monitoring, magnesium sulfate infusion, and anti-hypertensive drugs as needed for systolic BP > 160 or diastolic BP > 110 mmHg.[11] Delivery is required for worsening maternal or fetal condition. Patients who are not candidates for expectant management include women with eclampsia,

pulmonary edema, DIC, renal insufficiency, abruption, abnormal fetal testing, HELLP syndrome, or persistent symptoms of severe preeclampsia.

Early-onset preeclampsia is a different and more severe disease than late-onset preeclampsia. Placental pathology in early-onset disease is characterized by hypoplasia and vascular lesions of insufficiency, while late-onset preeclampsia is characterized by inflammation and placental hyperplasia.[12] Early-onset preeclampsia is less common than late-onset (0.3% versus 2.7%), but maternal mortality is higher with early-onset preeclampsia (42 per 100K deliveries with early, versus 11 per 100K with late, versus 4 per 100K with no diagnosis of preeclampsia) as is maternal morbidity (12.2 per 100 deliveries with early, versus 5.5 per 100 deliveries with late, versus 3 per 100 deliveries without preeclampsia).[13]

HELLP syndrome is a variant of severe preeclampsia. Administration of high-dose glucocorticoids (dexamethasone 10 mg BID for example) has been reported to improve maternal and fetal outcome, but without large multicenter trials to define the limits of benefit and any maternal or fetal risk. As a vasodilator, sildenafil (Viagra®) has been studied in an RCT as a treatment to prolong pregnancy.[14] The women receiving sildenafil 50 mg TID had lower blood pressures and required less anti-hypertensive therapy at lower doses. Umbilical artery Doppler studies also improved with no differences in adverse effects or perinatal morbidity versus placebo.

Use of Invasive Monitoring and Treatment of Hypertension

Invasive monitoring is rarely necessary in obstetric patients. "Critically ill obstetric patients differ from those usually encountered in medical-surgical intensive care units. They are likely to be younger, to have fewer major organ systems involved, to have fewer chronic illnesses, and to recover fully with supportive care." (Chest 1992) However, arterial lines are low risk and can be useful when blood pressures are consistently greater than 160/110 mmHg and when vasodilator infusions are used. They may also be helpful for patients with coagulopathy who need frequent blood draws, and when the patient is obese or has marked edema making venipuncture difficult. If pulmonary edema develops, the arterial line can be used to monitor arterial blood gases. Pulse waveform analysis (e.g., LiDCOplus™) can be used with an arterial line for hemodynamic monitoring as it correlates well with thermodilution measurements from a pulmonary catheter.[15]

In contrast, central venous monitoring carries more risks and has not been shown to affect outcome. A CVP or PA catheter may be useful if there is cardiac failure or pulmonary edema, a large A-a oxygen gradient, or oliguria despite fluid administration and afterload reduction. Consider your nursing resources on L&D before initiating invasive monitoring however. Can the L&D nursing staff manage a CVP or pulmonary artery catheter on L&D, or will ICU admission be necessary? Other non-invasive options might be ultrasound to evaluate for pulmonary edema or trans-thoracic echocardiography (TTE) to evaluate cardiac dysfunction.[16]

The goal of anti-hypertensive therapy is to prevent pulmonary edema and cerebral hemorrhage by decreasing systolic blood pressure < 160 mmHg and diastolic < 110 mmHg. At the same time, treatment should not impair uteroplacental perfusion or cause fetal compromise. Systolic hypertension may be more important than diastolic for preventing stroke related to severe preeclampsia.[17] A review found that 93% of the strokes in their series were hemorrhagic, 54% of women died, and almost all who lived had severe permanent disability. All had systolic pressure >155 mmHg while only 12% had diastolic pressure >110. CVA's that occur with hypertensive disorders of pregnancy are associated with impaired cerebral autoregulation, which is reduced in preeclampsia and chronic hypertension, but lowest in chronic hypertension with superimposed preeclampsia.[18] Pregnancy-related strokes have increased over the past 20 years, and strokes in women with hypertensive disorders were associated with more frequent complications and death.[19]

The ACOG Committee Opinion entitled "*Emergent Therapy for Acute-Onset, Severe Hypertension with Preeclampsia or Eclampsia*" defines a hypertensive emergency as systolic pressure > 160 mmHg or diastolic pressure > 110 mmHg lasting 15 minutes or longer.[20] Previous work has shown hypertension is the most important predictor of cerebral hemorrhage or infarction and can result in maternal death. Aggressive treatment is imperative! Intravenous labetalol, PO nifedipine, and intravenous hydralazine are considered first-line treatments, and the document includes order sets for administration. Importantly for anesthesiologists, the document states that if these medications fail to control blood pressure, "emergent consultation with an anesthesiologist, maternal-fetal medicine subspecialist, or critical-care specialist to discuss second-line intervention is recommended."[20] A national group reported they had been able to reduce their maternal deaths from preeclampsia 5-fold by instituting a policy for automatic, rapid anti-hypertensive therapy for defined blood pressure elevations.[21]

Many agents are effective and safe to use as anti-hypertensives. Using non-invasive hemodynamic monitoring to determine whether the patient's hemodynamics are hyperdynamic or are characterized by elevated SVR and compromised cardiac output can be very helpful in choosing an anti-hypertensive medication. Trans-

thoracic echocardiography, bio-impedance devices or analysis of the arterial waveform have been described. Anti-hypertensives to consider in practice:

1. Hydralazine 5-20 mg is a popular choice in obstetrics because it is an arteriolar vasodilator that increases uterine and renal blood flow. However, it has an unpredictable onset and duration, causes reflex tachycardia and occasional dysrhythmias.
2. Labetalol decreases systemic vascular resistance without maternal tachycardia while preserving placental blood flow, however dosing and duration may be quite variable. It does not cause sympathetic blockade in the neonate. It can be transitioned to an oral form after delivery.
3. Calcium channel blockers such as nifedipine and nimodipine cause a rapid smooth fall in blood pressure while increasing renal perfusion and urine output. Nimodipine reverses cerebral vasospasm as measured by trans-cranial Doppler, and is well-tolerated by mother and fetus. However, calcium channel blockers cause uterine relaxation, making induction of labor more difficult and potentially causing atony and hemorrhage after delivery.
4. Nitroprusside has a fast onset, short duration, and preserves uterine blood flow. However, it leads to reflex tachycardia and has the potential for cyanide toxicity. It causes cerebral vasodilation that could increase intracranial pressure and it decreases hypoxic pulmonary vasoconstriction potentially leading to hypoxia. Finally, it is inconvenient to use and requires an arterial line, as does nitroglycerin.
5. ACE inhibitors and angiotensin receptor blockers are teratogenic and contraindicated in all trimesters of pregnancy. Avoid atenolol (IUGR concerns) and chronic diuretic therapy.[22]
6. Magnesium sulfate is not an anti-hypertensive and has no substantial long-term effect on blood pressure, but has other benefits. It attenuates the vascular response to pressor substances (either endogenous or exogenous) and dilates vascular beds by increasing prostacyclin release from endothelial cells, decreasing plasma renin activity, and decreasing ACE levels. It also provides neuroprotection for premature fetuses less than 32 weeks.

Prevention and Management of Seizures / Eclampsia

Eclampsia has a maternal mortality rate of ~ 4% and a perinatal mortality rate of up to 30%. Seizures occur antepartum in 50% of patients, intrapartum in 25% and postpartum in 25%. Why do we use magnesium to prevent eclamptic seizures rather than other traditional anti-seizure medications? In large randomized clinical trials, magnesium has been proven superior to placebo (58% lower risk of seizures), phenytoin (no seizures in the magnesium group versus ~1% in the phenytoin group), diazepam (52% lower risk of recurrent convulsions), and nimodipine (risk of eclampsia was 3.2 times higher in the nimodipine group). No drug is superior to magnesium at preventing eclampsia.[23,24]

Magnesium therapy is not without complications however. It can cause maternal morbidity and unpleasant side effects. It has tocolytic properties that prolong labor and increase bleeding at delivery. It decreases fetal heart rate variability, depresses maternal and neonatal neuromuscular function, and can cause maternal respiratory depression and cardiac toxicity at excessively high blood levels. Clearance is reduced with renal insufficiency, and signs of toxicity are only partially reversed with intravenous calcium. Consider dialysis for life-threatening overdose.

Since major complications of preeclampsia occur in the 25% of patients with the severe form of the disease, should mild preeclampsia even be treated with magnesium? What is the risk/benefit ratio for the mother? A decision analytic model of magnesium therapy or no magnesium therapy found that 400 women with mild preeclampsia need to be treated to prevent one seizure. The number needed to treat to prevent a seizure (NNT) fell to 129 in severe preeclampsia, and to only 36 in severely preeclamptic women who had symptoms such as headache, visual disturbances or epigastric pain.[25] When an eclamptic seizure occurs, the following steps should be taken:

- Administer high flow supplemental oxygen by mask and place a pulse oximeter to assure adequate maternal oxygenation.
- Turn the patient to full left or right lateral position and have suction immediately available.
- Although you can give a small dose of propofol or a benzodiazepine to terminate the seizure, avoid poly-pharmacy and long-lasting medications so that a neurologic exam can be done as soon as possible.
- Administer an additional 2-gram magnesium bolus to assure levels are therapeutic.
- Monitor the fetus if possible, but realize that heart rate abnormalities are common during a seizure and usually resolve soon after the seizure is terminated. Do not intervene to deliver emergently unless abruption or cord prolapse has occurred.

- Consider imaging with CT or MRI to rule out a cerebral hemorrhage if seizures are recurrent or focal, if seizures occur despite therapeutic and repeated magnesium dosing, or if there is decreasing level of consciousness after the seizure.
- Although eclampsia is an indication for delivery, it is not an indication for cesarean delivery. When eclamptic patients were randomized to vaginal delivery or cesarean, there was no difference in maternal or newborn adverse events.[26] Consider whether induction or augmentation of labor is feasible.

Anesthetic Management During Labor and Delivery

When the decision has been made to proceed with delivery, the anesthesiologist must have plans in mind for three potential scenarios: 1) labor followed by a spontaneous or instrumented vaginal delivery, 2) trial of labor followed by an urgent or emergent cesarean for fetal or maternal indications, and 3) planned cesarean for the patient who is not a candidate for trial of labor. All plans must take into account whether neuraxial techniques are appropriate based on platelet count or other measures of coagulopathy.

Labor Analgesia

The advantages of neuraxial analgesia for labor are numerous. It provides the best quality of pain relief, attenuates hypertensive responses to pain and reduces circulating catecholamines. Two studies have compared the use of intravenous patient-controlled opioids (IV PCA) to epidural analgesia for women with severe preeclampsia. In the first, 738 women were randomized to IV PCA or epidural, and cesarean delivery rates were similar.[27] Neonates in the IV PCA group required more naloxone (12% versus 1%), but women in the epidural group had a longer second stage of labor, more forceps deliveries and required ephedrine more often (11% versus 0%). Not surprisingly, epidural pain relief was superior.[25] Results were similar in the second study.[28] They found no difference in cesarean delivery rates, but neonates were more likely to receive naloxone in the opioid group (54% versus 9%), and epidural patients had significantly better pain relief but required more ephedrine (9% versus 0%). Perhaps most importantly, there were no differences in preeclampsia-related complications when epidural analgesia was used.[26] ACOG makes a strong statement in their Practice Bulletin: "With improved techniques over the past two decades, regional anesthesia has become the preferred technique for women with severe preeclampsia and eclampsia – both for labor and delivery. A secondary analysis of women with severe preeclampsia in the NICHD trial of low-dose aspirin reported that epidural anesthesia was not associated with an increased rate of cesarean delivery, pulmonary edema or renal failure."[2]

Fluid Management

Fluid management has been controversial, with obstetricians wanting to restrict fluids and anesthesiologists wanting to administer fluids, however the obstetric view is probably correct. The vasculature in preeclamptic patients has been described as contracted and porous due to endothelial damage, but not under-filled. In addition to endothelial damage, the colloid oncotic pressure is low in pregnancy, and even lower in preeclamptic patients with proteinuria. Crystalloids and colloids readily leak out, increasing the risk of postpartum pulmonary edema. Typical obstetric management is to "run dry" at 80-100 ml per hour total fluid intake including magnesium and oxytocin infusions. Anesthetic fluid management should complement theirs, using conservative preload for surgical neuraxial anesthesia and no preload for labor analgesia. Many studies including a systematic review have shown little if any benefit of preloading to prevent hypotension during obstetric regional anesthesia.[29] Do not require fluid preload when dilute local anesthetic solutions with opioid are used.

Coagulopathy and Platelet Counts

What is the frequency of lab abnormalities in preeclampsia? In a large study of women with hypertension, abnormal labs occurred in 7.3% of hypertensive patients.[30] In mild preeclampsia only 5% of women had abnormal studies, as compared with 9% with severe preeclampsia and 12% with severe preeclampsia plus clinical signs of end-organ dysfunction. Women with mild disease and no signs of end-organ involvement may not require routine labs since 95% will be normal.[30] Despite years of concern and study, there is still no test for platelet function and no specific platelet count that predicts bleeding into the neuraxis after regional anesthetic techniques. For patients with preeclampsia, many anesthesiologists are comfortable with platelet counts as low as 75,000 provided the count is stable and not falling, and that there are no signs of clinical bleeding at venipuncture sites, gums, etc. Thromboelastography (TEG) can add information if the test is available, but there is still no cut-off value for any TEG variable that predicts complications. Since pregnancy is a thrombophilic state, parturients have tremendous reserve before developing a coagulopathy. A review of 1.7 million spinal or epidural blocks found that complications were more common after epidural than spinal anesthetics, and that obstetric patients were **less** likely

than surgical patients to have an injury (1: 25,000 obstetric patients versus 1:3600 after surgical epidurals in females).[31] There were two obstetric patients in their series that developed a neuraxial hematoma, for an incidence of 1: 200,000. One occurred after a spinal and the other after epidural catheter removal; both patients had HELLP syndrome. This low incidence is reassuring, but balance the risk-benefit ratio for each case and each patient.

Factors that might support using a regional technique even with borderline labs would include a worrisome airway exam, the prospect of a lengthy induction of labor, and the rarity of an epidural hematoma. Factors that would support avoidance of regional anesthesia and use of IV opioids or general anesthesia would be clinical signs of bleeding, a rapidly worsening platelet count, the need for an urgent cesarean and a good airway. If you feel that neuraxial analgesia is not appropriate, remember that anesthesiologists are consultants in pain management. Our obstetric colleagues may appreciate help with an IV regimen for the patient's labor analgesia. For example, fentanyl can be used in an IV PCA as follows: give an IV bolus loading dose of 2-3 µg/kg to initiate analgesia. Set the PCA pump for a 50 µg incremental bolus, 10-minute lockout interval and no basal rate. As labor progresses and titration is needed, decrease the lockout from 10 to 5 minutes, then increase the bolus dose from 50 to 75 µg. Remifentanil has also been used successfully for patient-controlled analgesia during labor.[32]

Cesarean Anesthesia

The choices for cesarean anesthesia are epidural, spinal (or combined spinal-epidural) and general. In the past, spinal anesthesia was avoided because of concerns that hypotension would be more severe and less treatable than that seen after sympathetic block after an epidural anesthetic. However, a comparison of women with severe preeclampsia to healthy women, all having cesarean delivery with a spinal anesthetic, found that preeclamptic women actually had less hypotension (17% versus 53%) despite receiving less fluid preload and (by chance) a larger dose of bupivacaine in their spinal.[33] A randomized comparison of spinal or epidural anesthesia for cesarean delivery in women with severe preeclampsia found that although hypotension was more frequent after spinal and required slightly more ephedrine, the duration of hypotension was short and easily managed, and neonatal outcomes were similar in both groups.[34]

Regardless of the choice of neuraxial technique (spinal or epidural), pressors must be immediately available to treat even mild hypotension since these fetuses may not tolerate any decrease in uteroplacental perfusion. Although not studied in severe preeclampsia, clinical studies in healthy parturients have consistently shown that use of α-agonists such as phenylephrine produce better umbilical pH values in the newborn than ephedrine.[35] If maternal heart rate is above 70, choose phenylephrine as the first-line pressor agent.

If general anesthesia is chosen, focus on attenuating hypertensive responses during laryngoscopy and intubation, managing a potentially difficult edematous airway, and treating complications related to magnesium therapy such as uterine atony and maternal weakness. Cerebral autoregulation is significantly reduced in women with preeclampsia, with no correlation between the autoregulation index and blood pressure.[36] A number of adjuncts to rapid sequence induction have been described and used successfully to control hypertension associated with laryngoscopy, e.g. esmolol, labetalol, nicardipine, remifentanil[37] and nitroglycerin. Include at least one adjunct as part of a rapid sequence induction, or have them immediately available to treat hypertension if it occurs.[38] Airway management may be difficult. The laryngeal mask airway (LMA) has been used in the setting of HELLP syndrome when there was inability to intubate or ventilate.[39] Postoperatively, this patient was even ventilated in the ICU using the LMA.

Magnesium therapy has anesthetic interactions such as skeletal muscle weakness. If the mother exhibits muscle weakness *prior* to induction (i.e., can she do a 5-second head lift before her anesthetic?), it may be best to discontinue the magnesium sulfate infusion during the case and let her magnesium level decrease. However, ACOG recommends continuing the magnesium infusion intraoperatively if possible so that the patient retains a therapeutic level and doesn't require re-bolus.[2] Non-depolarizing muscle relaxants should be avoided. If she does not meet criteria for safe extubation at the end of the cesarean, she may require a brief period of mechanical ventilation until she is strong enough to protect her airway. Magnesium is a uterine relaxant, and additional oxytocic medications such as misoprostol or prostaglandin $F_{2\alpha}$ should be available to treat uterine atony after delivery in addition to oxytocin.

Postpartum Care

After delivery patients will require intense monitoring on L&D. All patients will receive 24 hours of magnesium sulfate for seizure prevention. They should have compression stockings for thromboprophylaxis. If general anesthesia was used, consider transversus abdominis plane (TAP) blocks to supplement analgesia.[40] The mother may need both acute and long term blood pressure control with anti-hypertensives. Fluid mobilization will begin to occur during the first 24 hours postpartum, and this is when she is most at risk for pulmonary edema. Monitor urine

output, lung fields and pulse oximetry. Thrombocytopenia may not resolve for several days. If she has an epidural catheter in place, decide when removal is appropriate based on her platelet count and coagulation studies. About a third of eclamptic seizures occur postpartum, and are associated with severe morbidity.[41] Many eclamptic patients do not have an antepartum diagnosis of preeclampsia, but most have prodromal symptoms such as headache and visual changes. If called to evaluate a postpartum headache, consider late-presenting preeclampsia in your differential. In a survey of pregnant women presenting to the Emergency Department with acute headache, 65% had a primary headache diagnosis (91% migraine), but 35% had a secondary cause for the headache and preeclampsia was the most common secondary diagnosis.[42]

Prognosis After the Diagnosis of Preeclampsia

Does development of preeclampsia provide a marker for maternal disease risks later in life? A growing literature indicates that pregnancy is a form of "stress test" that may predict later health issues in the mother.[43] Decades of follow-up of women who had hypertension during pregnancy (even gestational hypertension) found an elevated risk of cardiovascular disease and chronic hypertension[44] as well as other health issues such as Alzheimer's and all-cause mortality.[45] ACOG recommends better long term follow-up of preeclamptic women by their primary care physicians. The implications of this disease do not end at delivery. Are primary care providers aware that preeclampsia increases later risk of cardiovascular disease? A study found gynecologists were more likely to ask women about their pregnancy history, but didn't get appropriate testing for cardiovascular disease.[46] Internists got the appropriate testing, but didn't ask about pregnancy history. Both groups need additional education.

New Guidelines from ACOG

In 2013 the ACOG Task Force on Hypertension in Pregnancy updated guidelines.[2] Highlights include:

1. There are no predictive tests or preventive measures to use, and there are no treatments except delivery.
2. Features of severe preeclampsia are BP $\geq$ 160/110, platelets < 100K, elevated liver function tests or epigastric pain, creatinine > 1.1, pulmonary edema and headache or visual changes. Proteinuria has been eliminated because it has no effect on outcomes.
3. Deliver at 37 weeks if no severe features are present and by 34 weeks with severe features – after steroids for fetal lung maturity.
4. During cesarean, continue magnesium infusion and use neuraxial anesthesia if possible.
5. Avoid NSAIDs if hypertension persists postpartum.
6. Discharge instructions should include warnings about signs and symptoms of postpartum preeclampsia.

In Conclusion:

- Be conservative with fluid preload before neuraxial procedures. Consider eliminating.
- Normalize low blood pressure with phenylephrine in preference to ephedrine.
- The goal for management of blood pressure is to keep maternal pressure near baseline to sustain uteroplacental perfusion, but < 160 mmHg systolic to prevent cerebrovascular complications.
- Use platelet count trends and your clinical judgment. There is no absolute platelet count or TEG value to use as a cut-off to assure the safety of neuraxial anesthetic techniques.
- Spinal anesthesia for cesarean delivery is safe. Limit fluid preload and maintain her blood pressure close to her baseline levels.
- Actively participate as part of the L&D team caring for high risk obstetric patients.[47]

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Perioperative Delirium: Making Sense of All the Confusion

Christopher G. Hughes, MD **Nashville, TN**

INTRODUCTION

Delirium occurs when a patient experiences fluctuation in mental status caused by acute cerebral dysfunction. All hospitalized patients are at risk for the development of delirium, and patients in the perioperative setting are no exception. The risk of developing delirium appears dependent on age, preexisting comorbid conditions, severity of concurrent illness, and severity of the surgical process.[1] Studies in surgical patients focusing on delirium in the first few postoperative days have found significant associations with increased length of stay, higher cost of care, readmission to the hospital, higher rates of institutionalization after discharge, prolonged cognitive impairment, and increased mortality.[2-6] Because delirium occurs commonly and is associated with worse outcomes, an understanding of its disease process, risk factors, and management is essential for an anesthesiologist.

DEFINITION AND DIAGNOSIS

To diagnose perioperative delirium, it is important to understand the definition: a disturbance in the ability to direct, focus, sustain, and shift attention coupled with a change in cognition (memory deficit, disorientation, or perceptual disturbances) which cannot be accounted for by a neurocognitive disorder or a severely reduced level of arousal.[7] Changes in attention and cognition are acute in onset, fluctuate, and may include hypoactive and/or hyperactive psychomotor activity. Hypoactive delirium is characterized by slowed mentation, lethargy, and a decrease in movement. Hyperactive delirium is characterized by agitation and restlessness. Another form of delirium common in the perioperative setting is emergence delirium, which typically refers to agitation after discontinuation of an anesthetic. PACU delirium is mental status changes that occur after emergence but before PACU discharge criteria are met. Postoperative delirium occurs when mental status changes take place after the patient meets PACU discharge criteria, whether on the hospital ward or in the ICU.

The diagnosis of delirium is very important but can be challenging in the perioperative setting due sedative and analgesic medication administration and emergence from general anesthesia. The gold standard for delirium diagnosis is to have the patient evaluated by a psychiatrist using *The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* criteria.[7] Since this is not routinely feasible in most hospitals, there are validated instruments to aid clinicians in the diagnosis. There are no validated instruments, however, specifically focusing on assessment of delirium in the PACU setting. The key components of these validated instruments can be used to aid in the diagnosis no matter the perioperative stage. The first thing a clinician must do is assess a patient's level of arousal. Delirium assessment cannot occur if the patient is unresponsive to voice. The most common arousal scales used are the Richmond Agitation Sedation Scale (RASS)[8] and the Sedation Agitation Scale (SAS).[9] After the patient has achieved a level of arousal that allows for response to verbal stimuli, the Confusion Assessment Method (CAM),[10] the 4AT,[11] the Nursing Delirium Symptom Checklist (NuDESC),[12] the Confusion Assessment Method for Intensive Care Unit (CAM-ICU),[13] the Intensive Care Delirium Screening Checklist (ICDSC),[14] or another validated assessment tool can be utilized. Importantly, most delirium goes undiagnosed if a regular screening tool is not used. The NuDESC and CAM-ICU tools have been the most studied tools in the PACU, but neither is very sensitive for PACU delirium.[15] Their specificity, however, was found to be >90%. Therefore, if a patient tests positive on one of these assessment tools, the diagnosis of delirium is very likely to be correct. Finally, current research is examining delirium severity scales through modification of these assessment tools (**Table 1**). The CAM-S tool to quantify the severity of symptoms has been validated, and severity as determined by the CAM-S has been associated with both in-hospital and post-discharge outcomes.[16] The CAM-ICU-

TABLE 1. DELIRIUM SEVERITY FOR CAM-S AND CAM-ICU-7

Feature	Grading
Fluctuation of mental status	0 for absent 1 for present
Inattention	0 for absent 1 for inattention 2 for severe inattention
Altered level of consciousness	0 for absent (RASS 0) 1 for mild altered level 2 for severe altered level
Disorganized thinking	0 for absent 1 for mild disorganized thinking 2 for severe disorganized thinking

7 severity tool has been validated in critically ill patients, and severe delirium on the CAM-ICU-7 has been associated with higher odds of death.[17]

PREVALENCE

Delirium prevalence in the perioperative setting varies widely depending on the patient population, definition, and assessment tool utilized. In a cohort of 400 patients undergoing non-cardiac surgery, hyperactive agitated arousal from anesthesia was found to occur in 19% of patients.[18] When using the CAM-ICU, 37% of patients had delirium upon on arrival to the PACU, 47% of whom had hypoactive signs and 53% of whom had hyperactive signs. During the PACU stay prior to meeting PACU discharge criteria, 16% of patients had delirium, 92% of which had hypoactive signs. After meeting PACU discharge criteria, 5% of patients had delirium.[18] In a smaller study of patients > 70 years old, 45% of patients had delirium *after* completing recovery from anesthesia.[2] Postoperative delirium has been reported at approximately 50% after cardiac, orthopedic, and major non-cardiac surgery (**Table 2**) and typically occurs on the first or second day after surgery.[1] If patients are admitted to an ICU after surgery and require mechanical ventilation, delirium prevalence can be as high as 80%. On the ward and in the ICU, hypoactive delirium is much more common than the more clinically apparent hyperactive delirium.

TABLE 2. RATES OF DELIRIUM PER SURGERY CLASSIFICATION

Surgery	Rate
Otolaryngological	12%
General	13%
Aortic	29%
Orthopedic	40%
Major Abdominal	50%
Cardiac	52%

ETIOLOGY AND RISK FACTORS

The pathophysiology of delirium is poorly understood with many proposed mechanisms depending on the patient and the clinical situation. This includes systemic inflammation, nervous system inflammation, endothelial and blood brain barrier dysfunction, cholinergic deficiency, and disturbances in neurotransmitters such as serotonin and norepinephrine.[19] Studies have also shown neuroanatomical changes associated with delirium, including brain atrophy and white matter changes.[20,21]

There are known risk factors that are important for identifying high risk patients (**Table 3**). In general, these include, and are not limited to, increasing age, pre-existing cognitive impairment, and increasing comorbid medical conditions.[22]

Understanding the precipitants can also be extremely important to change clinical strategies in order to minimize the occurrence of delirium. In addition, risk factors of postoperative delirium reported in the literature appear to be influenced by the severity of the surgical insult and by the exposure to sedative and/or analgesic medications during the perioperative period. Benzodiazepine exposure is known to be associated with an increased risk of emergence and postoperative delirium.[23,24] Opioid administration has been associated with delirium in the postoperative and ICU settings;[18,25,26] however, data on this association is inconsistent as others have shown opioids to be protective (or have no effect) with regard to delirium when used to appropriately control pain.[27-29] One thing that has been shown to increase perioperative delirium rates, repeatedly, is increasing pain scores.[30]

TABLE 3. DELIRIUM RISK FACTORS AND PRECIPITANTS

Risk Factors	Precipitants
Increasing age	Infection
Pre-existing cognitive impairment	Dehydration
Frailty	Electrolyte abnormalities
Congestive heart failure	Acute kidney failure
Acute myocardial infarction	Acute liver failure
Mechanical ventilation	Hypoxemia
Poly-trauma	Ethanol/drug withdrawal
Metabolic acidosis	Fragmented sleep
ASA >3 classification	Central nervous system insults
Emergency vs. elective surgery	Benzodiazepines, incl premedication
Open vs. endovascular surgery	Deep sedation
Increased surgical duration	Poor pain control
Existing coma or delirium	Opioid administration?

DELIRIUM PREVENTION

Many risk factors for delirium are unable to be modified by perioperative providers, but several preventative strategies have been demonstrated to reduce the incidence of delirium. Prevention of delirium is of utmost importance because the number of evidence-based treatment options for delirium is minimal.

Anesthetic Techniques

The evidence is inconclusive regarding the effects of anesthesia type or depth of anesthesia on the development of postoperative delirium. There was not any difference in delirium rates when comparing total intravenous propofol general anesthetic compared to desflurane.[31] Similarly, no difference was found in early cognition when comparing total intravenous propofol general anesthetic and sevoflurane[32] or when comparing sevoflurane and desflurane.[33,34] Spinal anesthesia combined with lighter sedation in elderly patients undergoing hip surgery was shown to decrease the incidence of postoperative delirium when compared to spinal anesthesia with deeper sedation.[35] Other research has shown that monitoring depth of anesthesia was associated with less over sedation and also with less postoperative delirium.[36] In a Cochrane review, regional anesthesia in patients undergoing hip surgery resulted in a potential decrease in postoperative confusion when compared to general anesthesia.[37] However, a large prospective study of elderly hip surgery patients did not find a decreased risk of postoperative delirium with regional anesthesia vs. general anesthesia,[38] and neither did a meta-analysis.[39] Importantly, the results of these studies in patients with lower extremity orthopedic procedures may not be generalizable to other surgical procedures. Current clinical guidelines[40] for postoperative delirium prevention in the elderly state that regional anesthesia can improve pain control and help prevent delirium, as studies have shown an association between poor pain control and higher rates of delirium. A study of femoral nerve blockade in addition to patient controlled analgesia demonstrated a lower incidence of postoperative delirium after total knee replacement.[41] The addition of non-opioid adjuncts for perioperative pain control has also shown promise at reducing the rates of perioperative delirium. Patients undergoing spine surgery were randomized to gabapentin or placebo prior to surgery in a small randomized controlled trial; the patients who received gabapentin had reduced rates of delirium.[42] In fast-track knee and hip arthroplasty, patients whose primary pain management plan was gabapentin, acetaminophen, and celecoxib were found to have low incidence of delirium.[43] This multi-modal analgesic plan is a key component of any enhanced recovery after surgery (ERAS) pathway, and lower rates of delirium have been reported in colonic surgery patients when on a ERAS pathway with low opioid exposure.[44] Thus insuring adequate pain control through regional techniques and non-opioid adjunct medications seem beneficial with regard to delirium outcomes.

Cardiac Surgery

Numerous studies have examined agents to prevent delirium after cardiac surgery. To potentially reduce the subsequent inflammatory response to cardiopulmonary bypass and surgery, ketamine and dexamethasone administration have been studied. Provision of ketamine during anesthesia induction reduced the odds of developing delirium compared to placebo in a small randomized controlled trial.[45] Administration of dexamethasone upon induction of anesthesia did not reduce the incidence or duration of delirium after cardiac surgery compared to placebo in a much larger randomized controlled trial.[46] To test the hypothesis that increased cholinergic activity would decrease delirium after cardiac surgery (since low cholinergic activity and anticholinergic medications have been associated with delirium), a randomized controlled trial of prophylactic rivastigmine vs. placebo starting the night prior to surgery was performed but found no difference in the incidence of postoperative delirium.[47] One study found that a single dose of sublingual risperidone, once the patient had regained consciousness in the ICU, reduced the incidence of delirium when compared to placebo.[48] Another study of risperidone in elderly patients requiring cardiac surgery found that repeated doses could prevent the development of delirium in patients already exhibiting some signs of acute brain dysfunction (referred to as subsyndromal delirium).[49] These positive results with risperidone need to be confirmed in additional larger cohorts before routine administration can be recommended. Finally, the use of dexmedetomidine for sedation after cardiac surgery has been shown to improve delirium outcomes when compared to morphine- or propofol-based sedation regimens.[50-52]

Pharmacologic Prophylaxis

Studies investigating whether prophylactic antipsychotic administration reduces the incidence or duration of delirium have had mixed results. Perioperative haloperidol prophylaxis for up to 6 days (up to 3 days prior to and 3 days after surgery) did not affect delirium incidence but did decrease delirium duration compared to placebo in a randomized controlled trial in elderly hip surgery patients at intermediate or high risk for postoperative delirium.[53] The choice of anesthetic was not reported or accounted for in the analyses. In elderly elective surgery patients, haloperidol prophylaxis for 3 days in the postoperative period *increased* the incidence of delirium (severity and duration were unaffected).[54] Perioperative olanzapine prophylaxis decreased the incidence but did not affect the duration or severity of delirium in elderly elective joint replacement surgery patients.[55] In a randomized controlled

trial in elderly patients admitted to the ICU after non-cardiac surgery, low dose haloperidol bolus followed by an infusion decreased the incidence of delirium compared to placebo only after intra-abdominal surgeries.[56] A before-after study of haloperidol as prophylaxis in ICU patients deemed high risk for delirium showed significantly less incidence and duration of delirium,[57] but a more recent randomized controlled trial showed no difference in delirium duration in patients receiving intravenous haloperidol prophylaxis or placebo.[58] Patients receiving haloperidol had less agitated delirium but increased oversedation.[58]

Prophylactic dexmedetomidine infusion (as opposed to dexmedetomidine infusion for sedation) has been studied as a method to prevent postoperative delirium. A study randomized elderly patients with normal cognition or mild cognitive impairment undergoing joint replacement surgery to dexmedetomidine or normal saline infusion during surgery.[59] Both normal and cognitively impaired patients had decreased incidence of postoperative delirium with dexmedetomidine vs. normal saline. A large double-blind, placebo-controlled trial in two tertiary-care hospitals enrolled patients >65 years old admitted to the ICU after non-cardiac surgery and randomized them to either a sub-sedative, low dose dexmedetomidine infusion or placebo.[60] Patients requiring mechanical ventilation received propofol or midazolam to achieve sedation targets prior to study drug administration. Patients received study drug from ICU admission until 8:00 AM the following morning. They found that the incidence of postoperative delirium was significantly lower over the first 7 days of their hospitalization in the dexmedetomidine group.[60] Interestingly, the patients receiving the low dose dexmedetomidine infusion had lower pain scores, and the reduction in delirium remained when stratifying patients by whether or not they required postoperative mechanical ventilation.

Though cholinergic depletion is thought to play a role in delirium development, acetylcholinesterase inhibitors such as rivastigmine and donezepil have had disappointing results with regard to delirium.[47,61-63] They have not been shown to decrease incidence or duration of delirium. The pleiotropic anti-inflammatory effects of statin medications have been of interest given the potential role of inflammation in delirium, but data are conflicting with regard to the effects of statins on delirium. In cardiac surgery patients with low delirium incidence, preoperative statin use has been associated with a reduced incidence of postoperative delirium in one study,[64] but another found no difference in delirium according to preoperative statin use.[65] In elderly elective surgery patients, preoperative statin use has been associated with an increased risk of postoperative delirium.[66] Preadmission statin use did not affect delirium in a cohort of critically ill patients,[67] but statin therapy while in the ICU has been shown in two studies to be associated with lower overall risk of delirium.[67,68] Also, increasing duration of statin discontinuation in chronic statin users increased the odds of developing delirium, potentially from a rebound pro-inflammatory state from statin discontinuation.[67] A randomized controlled trial of rosuvastatin versus placebo in acute lung injury patients, however, found no effect of rosuvastatin therapy on days with delirium.[69]

Intensive Care Unit Management

One hospital setting with established successful prevention techniques for delirium is the ICU. Sedative regimens that focus on targeted arousal levels and light sedation have positively affected the rates of delirium, and exposure to sedative medications and deeper levels of sedation have been associated with increased risk of delirium.[22] The use of dexmedetomidine for sedation during mechanical ventilation has improved delirium outcomes in randomized controlled trials when compared to lorazepam, midazolam, propofol, and morphine.[51,52,70,71]

Sleep hygiene is important to the prevention of perioperative delirium, as fragmented sleep has been associated with increased rates of delirium.[22] A decrease in the incidence of ICU delirium has been demonstrated when sleep disruptions are minimized and normal circadian rhythms are promoted.[72] No association was seen, however, between daily perceived sleep quality rating and transition to delirium.[73] Dynamic light application has been shown to restore circadian rhythms but was ineffective in reducing delirium in ICU patients.[74] Non-pharmacological sleep aids should be used when capable and alternative sleep medications used only when necessary. Interest in the role of sleep disturbances in delirium has led to studies investigating melatonin as an agent for delirium prevention. Studies investigating the benefit of prophylactic melatonin for delirium have had conflicting results.[75] In the perioperative setting, a double-blind randomized controlled trial of melatonin vs. placebo in patients with hip fracture did not demonstrate a difference in incidence of delirium.[76] A systematic review concluded that sleep interventions may be a promising means by which to improve delirium but that current research is limited by varied methodologies and significant bias.[77]

Early physical and occupational therapy has been demonstrated to reduce ICU and in-hospital delirium. Therapy typically progresses from passive range of motion to active range of motion, exercise in bed, sitting, standing, and walking depending on a patient's sedation level and physical abilities. A randomized controlled trial of daily sedation interruptions paired with physical and occupational therapy vs. usual care in hemodynamically stable medical ICU patients found a reduction in ICU and hospital duration of delirium by 2 days in the early therapy

group.[78] More recently, a randomized controlled trial of early goal-directed mobilization vs. usual care in surgical ICU patients found a reduction in the incidence of ICU delirium and an increase in ICU delirium-free days.[79]

Multicomponent Intervention

Multicomponent bundles combining evidence-based prevention techniques have also been shown to reduce delirium rates even further. Multicomponent prevention protocols that include reorientation, continuity of caregivers, decreased use of restraints, removal of catheters, providing hearing aids and eye glasses, and geriatrics consultation have been found to reduce delirium incidence and the total number of days of delirium in multiple studies of surgical and medical non-ICU patients.[75,80,81] In the ICU, bundles involving frequent assessment and control of pain, awakening and breathing trial coordination, light sedation, minimizing benzodiazepine use, delirium monitoring and management, and early mobility (i.e., the ABCDEF bundle) have been advocated to improve outcomes associated with delirium. A before-after trial of the implementation of this type of bundle found less delirium with a significant independent effect of the bundle on decreasing delirium.[82] A large scale implementation study of the ABCDEF bundle across multiple hospitals found that increased bundle compliance was associated with improved survival and increased the number of days alive without delirium or coma.[83]

Recommended strategies to reduce delirium in the perioperative setting are listed in **Table 4**.

TABLE 4. PERIOPERATIVE CARE STRATEGIES TO REDUCE DELIRIUM

Avoid or minimize precipitating medications (e.g., benzodiazepines, meperidine, anticholinergics)
Insure adequate pain control through regional techniques and non-opioid adjuncts
Light sedation for monitored anesthetic care when able
Avoidance of oversedation with general anesthesia
Restore hearing aids and eye glasses, prompt removal of catheters and restraints
Attention to hydration and electrolytes
Restart home statin therapy
Dexmedetomidine use and light-sedation techniques for sedation
Early mobilization
Multicomponent prevention bundles
Consultation services for elderly high-risk patients

DELIRIUM TREATMENT

Specific pharmacological agents for the treatment of delirium are not supported by definitive guidelines or large clinical trials. Their use should be restricted to the patient who has failed non-pharmacologic prevention strategies and who is a risk to self or others. The most popular pharmacologic treatments are antipsychotic medications (e.g., haloperidol, olanzapine, quetiapine) and dexmedetomidine. However, none of those agents are FDA-approved for the treatment of delirium. In one pilot study of ICU patients, there was no difference in delirium-free days amongst placebo vs. haloperidol vs. ziprasidone.[84] When haloperidol was compared to olanzapine for delirium treatment, there was no difference in length of delirium.[85] In a small study of patients who required intravenous haloperidol, subjects were randomized to receive placebo vs. quetiapine in addition to the haloperidol.[86] The quetiapine group had a faster resolution of the first episode of delirium.

A randomized controlled trial compared dexmedetomidine to placebo in patients with critical illness that had otherwise resolved but for whom weaning from mechanical ventilation was prevented by hyperactive delirium.[87] Patients treated with dexmedetomidine had increased ventilator-free hours and faster resolution of their delirium symptoms. A non-randomized study examined the effectiveness of dexmedetomidine as a rescue therapy for non-intubated ICU patients with hyperactive delirium.[88] Patients whose agitated delirium failed to be controlled with intravenous haloperidol received dexmedetomidine. Patients whose agitated delirium improved after haloperidol received a haloperidol infusion. Patients receiving dexmedetomidine had a higher percentage of time at target sedation, less over-sedation, and a shorter ICU length of stay without increased incidence of hemodynamic side effects. The other key conclusion from this study was the overall failure rate of haloperidol (43%), demonstrating the limited efficacy of antipsychotic agents in the treatment of delirium.[88]

The treatment strategies for delirium are sparse, and the evidence is lacking for a single pharmacologic approach. Prevention with non-pharmacologic means remains the best course of action. Agents that tend to be used to prevent or treat delirium affect the sensorium and have significant side effects. For example, antipsychotic agents can cause sedation, respiratory depression, prolonged QT intervals, and neuroleptic malignant syndrome; dexmedetomidine is administered by infusion often requiring ICU admission and can cause bradycardia. Additional studies are needed to examine the effectiveness of dexmedetomidine as a first-line therapy for the treatment of

delirium and with other alpha2-agonists administered orally or by intermittent intravenous bolus (e.g. guanfacine, clonidine) on delirium prevention and treatment.

SUMMARY

Delirium is a common problem in the perioperative setting associated with important clinical outcomes. An understanding of delirium risk factors, precipitating factors, and management is essential for an anesthesiologist in the perioperative care of patients. Importantly, screening and assessment tools are readily available for delirium diagnosis by non-psychiatric trained personnel to identify patients with delirium, including hypoactive and hyperactive subtypes. Prevention of delirium is of utmost importance because the number of evidence-based pharmacological options for delirium treatment is minimal, and those that exist have significant limitations.

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Myocardial Injury After Non-Cardiac Surgery (MINS)

Daniel I. Sessler, MD **Cleveland, Ohio**

In recent decades, intraoperative mortality has decreased by a factor-of-ten, even though we now care for much sicker and older patients.[1] Preventable anesthetic-related intraoperative mortality is now so rare that it is hard to quantify.[2] Postoperative mortality, in contrast, remains substantial. Overall 30-day postoperative mortality after non-cardiac surgery is about 1% in the United States, and about 2% amongst inpatients (outpatients rarely die).[3,4] To put this mortality in perspective, if the postoperative period were considered a disease, it would represent the third leading cause of death in the United States.[5] Myocardial infarction is the leading attributable cause of 30-day postoperative mortality, accounting for about a quarter of all deaths.[6]

Predicting postoperative myocardial infarctions remains challenging. The best pre-operative predictor appears to be NTproBNP,[7,8] but no predictor is sufficiently accurate for individual patients. Recent research has thus focused on prevention. Major trials, each with 7,000-10,000 randomized patients show that aspirin,[9] clonidine,[10] and avoiding nitrous oxide[11] do not safely prevent infarctions. Beta blockers reduce infarction risk about 30%, but at the cost of devastating strokes and an overall increase in mortality.[12] There is, however, a strong association between intraoperative hypotension and postoperative infarctions,[13-15] suggesting that supply-demand mismatch is an important cause of perioperative myocardial injury, although it is not an important cause of non-operative infarctions.

Worldwide, 8% of surgical inpatients >45 years of age sustain postoperative myocardial injury as defined by a troponin elevation that is due to an ischemic etiology, with only 42% of these events fulfilling the diagnostic criteria of the universal definition of myocardial infarction.[16] Only 14% of patients experiencing a perioperative myocardial infarction will have chest pain, and 65% are entirely clinically silent which means that they will go detected without routine troponin screening.[6,17,18]

We know from VISION (n=15,065) that postoperative myocardial infarctions are not restricted to high-risk patients.[19] The *only* enrollment criteria for this international prospective cohort were inpatient surgery age ≥45 years. Furthermore, participating hospitals deliberately enrolled a cross-section of patients making the results highly generalizable. In the VISION cohort, 8% of patients had elevated troponin concentrations after surgery, and 3.5% had centrally adjudicated myocardial infarctions based on clinical symptoms and/or consistent electrocardiographic or echocardiographic changes. It is thus obvious that risk is broadly distributed and that many postoperative infarctions will be missed if screening is restricted to patients with cardiovascular risk factors.

The term Myocardial Injury after Non-cardiac Surgery (MINS) recognizes that troponin elevations without a non-ischemic explanation (e.g., sepsis, pulmonary embolus) are clinically important — even in patients whose symptoms and signs do not meet the formal definition of a myocardial infarction.[19] Without troponin screening, 65% of the myocardial infarctions and 84% of the myocardial injuries after noncardiac surgery go unrecognized.[19] About 80% of troponin increases are completely asymptomatic — which is in marked contrast to non-operative myocardial infarctions which uniformly present with chest pain and/or shortness-of-breath. It is tempting to dismiss asymptomatic biomarker elevation as “troponitis” and assume that it is inconsequential; but this approach would be mistaken because 30-day mortality in patients with elevated postoperative troponin is similar *with and without* symptoms.[20]

Mortality at 30 days in patients with MINS is a striking 10%, which represents a five-fold increase from background risk. Mortality increases exponentially as a function of peak postoperative troponin concentration, ranging from 9% for fourth-generation troponin T (high-sensitive cardiac troponin T (hs-cTnT)) plasma concentrations of 0.03-0.29 ng/ml to 17% for concentrations ≥0.3 ng/ml. Moreover, it is not just mortality that is increased: a composite of nonfatal cardiac arrest, congestive heart failure, stroke, and death occurred at a rate of 2.4% in patients without MINS and 18.8% amongst those with MINS, a factor-of-eight increase.[20]

Amongst inpatients ≥45 years of age having noncardiac surgery, the number-needed-to-screen to detect MINS that would otherwise be missed is only about 15 patients. This is many fewer than for tests we do routinely for conditions that are far less deadly. Consistent with this logic, the Third Universal Definition of MI guidelines include: "Routine monitoring of cardiac biomarkers in high-risk patients after major surgery is therefore recommended."[16] In fact, troponin screening should not be restricted to high-risk patients because the incidence of MINS is 8% amongst a representative cross-section of surgical inpatients selected *only* for being at least 45 years old.[19]

The just-released Canadian Cardiovascular Society (CCS) guidelines on perioperative cardiac risk assessment and management of patients having noncardiac surgery gives a strong recommendation, based on moderate-quality evidence, for obtaining daily troponin measurements for 48 to 72 hours after noncardiac surgery in patients with a baseline risk >5% for cardiovascular death or nonfatal myocardial infarction at 30 days after surgery.[21] That would include patients: 1) with elevated NT-proBNP/BNP measurement before surgery; 2) a Revised Cardiac Risk Index score ≥1; 3) age 45 to 64 years with significant cardiovascular disease; or, 4) age ≥65 years. Troponin screening is similarly recommended by the American Heart Association for moderate-high-risk patients.

Troponin screening thus seems appropriate for most surgical inpatients ≥45 years of age, and certainly those who also have even a single cardiovascular risk factor. Troponin analysis can be included with routine morning blood sampling on the first, second, and third postoperative mornings while patients remain hospitalized. Screening thereafter is unnecessary since about 75% of postoperative myocardial infarctions occur within 48 hours after surgery[18] and because about 80% of all 30-day mortality occurs during the initial hospitalization.[22] That said, blood should immediately be sent for troponin analysis in any patients who has cardiovascular symptoms such as chest pain or shortness-of-breath. Non-ischemic causes of troponin elevation include end-stage renal disease, sepsis, and pulmonary embolism[16]; preoperative plasma troponin assays might help clinicians interpret subsequently elevated values.

Postoperative fourth-generation troponin T concentrations ≥0.03 ng/ml in the absence of alternative explanations should prompt a medical or cardiology consult. This recommendation is supported by evidence suggesting that intensification of cardiovascular therapy in patients with elevated postoperative troponin concentrations reduces the risk of subsequent cardiac events by about 40%.[23] Further work is required to establish the optimal thresholds for non-high-sensitivity troponin I assays and high-sensitivity troponin I and T assays.

Troponin testing is inexpensive and available worldwide. Compared with so many low-value perioperative tests, troponin has a number-needed-to-test of just 15 for a condition with a 10% 30-day mortality. That the cost is justified thus seems obvious, a conclusion supported by formal analysis.[24] In contrast, many common preoperative risk-assessment tests such as stress echocardiograms are expensive and provide little prognostic value.[6]

There are not currently published randomized trial results suggesting specific treatments for MINS. Nonetheless, potential benefits of troponin screening include cardiology consultation and patients: 1) being informed that they had myocardial injury and are thus at risk for future heart attacks; 2) potentially starting aspirin; 3) consideration for statin and/or ACE inhibitor therapy; 4) improved hypertension control, as necessary; and, 5) use of a "teachable moment"[25] to encourage lifestyle changes including smoking cessation, sensible diet, and enhanced exercise.

In summary, postoperative myocardial injury is rarely accompanied by symptoms — meaning that about 80% of cases will be missed without troponin screening (the number-needed-to-test is only about 15 patients). Mortality is 10% at 30 days, making myocardial injury a leading cause of short-term postoperative death, and mortality is nearly identical *with and without symptoms*. Asymptomatic troponin elevation is thus highly prognostic and cost effective. Fourth-generation troponin T concentrations ≥0.03 ng/ml should prompt a cardiology consult and interventions that might include aspirin, angiotensin converting enzyme inhibitors, and statins; blood pressure and heart rate control; and lifestyle enhancements including smoking cessation, exercise, and a healthful diet. How to safely prevent perioperative myocardial injury remains unknown. But in the mean time, avoiding hypotension (i.e., mean arterial pressure <65 mmHg) seems prudent.

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Radiation Safety for the Anesthesiologist and Pain Physician

Carlos A. Pino, M.D. **Burlington, Vermont**
Associate Professor, Department of Anesthesiology
University of Vermont College of Medicine

Introduction

Everyone on Earth is exposed to back ground radiation and it is estimated that if you combine cosmic radiation with medical, industrial and commercial sources, the average American is exposed to 6.2 mSv/year. Over the last two decades, pain physicians have increasingly used imaging to aid in performing procedures and anesthesiologists are progressively called to care for patients, in and out of the operating room, where radiation exposure is a hazard. The majority of the published studies focus on the exposure to surgeon or proceduralist, but very few publications address the exposure of the anesthesiologist. It has been estimated that pilots and flight attendants on ordinary aircrafts can receive annual doses around 10 mSv/year.

Definitions

Absorbed dose is the amount of energy deposited in the tissues at a specific point. It is measured in Gray (Gy) or Rads (1 Gy=100 rads).

Equivalent dose is a dosimetry metric that attempts to quantify biologic damage by different types of radiation. It is primarily used for radiation protection purposes and are only "approximate indicators" of potential harm. Equivalent dose is expressed in Sievert (Sv) (1 Sv = 100 rem). For example, alpha particles emitted in radiation therapy can do more damage than electrons emitted by x-ray imaging.

Effective dose is used to deal with the non-uniform dose distribution in the body and whether radiation is absorbed by a specific tissue. You need to take into account the type of radiation and the variable sensitivity of the organ (tissue weighting factors). Effective dose is expressed in Sieverts(Sv). The tissue weighting factor is the fractional contribution of each organ to the total whole-body radiation. (Tables 1 and 2)

Absorbed Dose ----------> Equivalent Dose ----------> Effective Dose

Radiation weighting factor

Tissue weighting factor

Table 1: Organ relative radiosensitivity (Tissue weighting factors) used by ICRP.

Tissue Weighting Factor	Organs	Detriment
0.12	Bone marrow; colon; lung; stomach; breast; adrenals, etc	Cancer
0.08	Gonads	Hereditary
0.04	Bladder, liver; esophagus, thyroid	Cancer
0.01	Skin; bone; brain	Cancer

Table 2: Organ dose (mGy) or Equivalent dose (mSv) for radiographic examinations.

Organ	Lateral Skull	PA Chest	AP Abdomen
Bone marrow	0.05	0.02	0.2
Lungs	<0.01	0.06	0.02
Stomach	<0.01	0.01	1.3
Colon	<0.01	<0.01	1.3
Breast	<0.01	0.01	0.01
Gonads	<0.01	<0.01	0.60
Effective Dose (mSv)	0.03	0.015	0.5

Radiation Biology - Interactions of radiations with tissue

Biologic effect of radiation depends on the total energy deposited in the cell (absorbed dose). The primary variable is that inherent to the cells at the time of irradiation, but there are other variables related to the radiation itself (type of radiation, absorbed dose, etc.). Damage to biologic systems always occurs first at the molecular level. Loss of molecular function will ultimately lead to cellular dysfunction and organ damage.

Direct vs. Indirect Ionizing Radiation

Direct action occurs when Compton electrons and photoelectrons ionize DNA molecules. It is responsible for less than 1/3 of the biological damage by ionizing radiation.

Indirect action occurs when Compton and photoelectrons interact with water in the cell to produce free hydroxyl radicals. These radicals can diffuse and damage target molecules, such as DNA. About 2/3 of the biologic damage

by x-rays is caused by indirect action.

Deterministic vs. Stochastic Effects

Deterministic effects are harmful tissue reactions that occur above a threshold dose (D threshold). For doses above the threshold dose, deterministic effects are expected to occur in all exposed individuals and are generally a direct result of cell destruction. Severity of of these effects may increase with increasing dose. Examples of deterministic effects include skin burns, epilation, eye cataracts, and sterility.

Skin: High skin doses generally occur at the point where an x-ray beam enters the patient. Below skin doses of 2 Gy, no effects are observed. Between 2 and 5 Gy erythema may occur, and above 5 Gy erythema will occur, so patients should be advised to perform self-exam in the following 2-10 weeks.

Epilation: The loss of hair can occur following irradiation of the scalp in high risk procedures. Below 3 Gy no loss of hair is expected. For scalp doses 3 to 6 Gy, temporary epilation may occur, with an onset at 2-3 weeks and complete regrowth at 6-12 months. At scalp doses of 7 Gy or above, epilation is likely to be permanent.

Cataract: As of 2011, the International Commission of Radiological Protection (ICRP) considers the threshold dose for cataract induction at 0.5 Gy. The latency period for the development of cataracts may be of several years and as the doses increase, the latency period may get shorter.

Sterility: Doses as low as 0.2 Gy can result in low sperm count and doses above 0.5 Gy can result in azoospermia. Permanent sterility in men requires a single dose of 6 Gy, and fractionated exposure to the gonads produce more damage than acute exposure. In females, doses for sterility (permanent ovarian failure) are dependent on age. Whereas 10 Gy can result in permanent sterility in prepuberty, only 2 Gy will do so in in premenopausal females.

Stochastic effects are random tissue reaction that have no threshold dose and the severity of these reactions are also independent of the radiation dose. In stochastic effects, the radiation dose only affects the probability of the event occurring. Examples of stochastic effects are carcinogenesis and hereditary effects.

Carcinogenesis: It is generally accepted that at higher (therapeutic) doses, radiation may result in cancer (i.e. radiation therapy for breast cancer and Hodgkin's lymphoma). Although there is still some uncertainty, growing evidence suggest that lower dose, such as those encountered in diagnostic applications, may result in increased carcinogenic risk (i.e. increased in leukemia and brain tumors in children who underwent CT in the UK).

Hereditary effects: these are based on animal data. Studies of children born to the A-bomb survivors have not shown any significant increased effects. In a population that excludes children, the hereditary risk is about 0.1% and in the entire population, the ICRP hereditary risk estimate is 0.2% per Gy. For conceptus deterministic risks, please see the ACR Practice Guidelines for Imaging Pregnant Women.

Radiation Safety for patients and staff

Approximately 400 million diagnostic exams are performed in the United State each year (table 3). Average exposure of the US population has increased from 0.6 mSv in the 1980s to 3 mSv in 2006. CT scans now account for 17% of all diagnostic x-ray examinations and half the population medical dose. Practitioners need to understand the magnitude of risk to benefit ratio of x-ray exam or x-ray guided procedure.

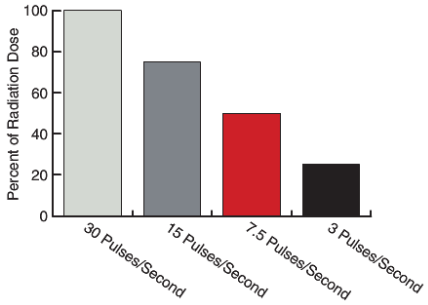
Table 3: Radiology exams performed in the United States in 2006

Type of exam	# performed (millions)	Average effective dose/patient exam (mSv)	Per Capita dose (mSv)
Radiography & Fluoroscopy	290	0.3	0.3
Interventional Radiology	20	8	0.4
Computed Tomography	70	7	1.5
Nuclear Medicine	20	13	0.8
Total	400	2.5	3.0

Radiation protection is aimed at preventing deterministic effects and minimizing risk of stochastic effects. As a general rule, the scatter dose at 1 meter is about 0.1% of the entrance skin dose. Methods to control radiation dose are decreasing exposure time, increasing distance from the source and shielding.

Exposure time should always be minimized. Fluoroscopy units have a 5-minute alarm that reminds operators of increasing exposure. Pulsed fluoroscopy should be used rather than continuous fluoroscopy whenever possible. Table 4 shows how using pulse fluoroscopy can reduce radiation dose.

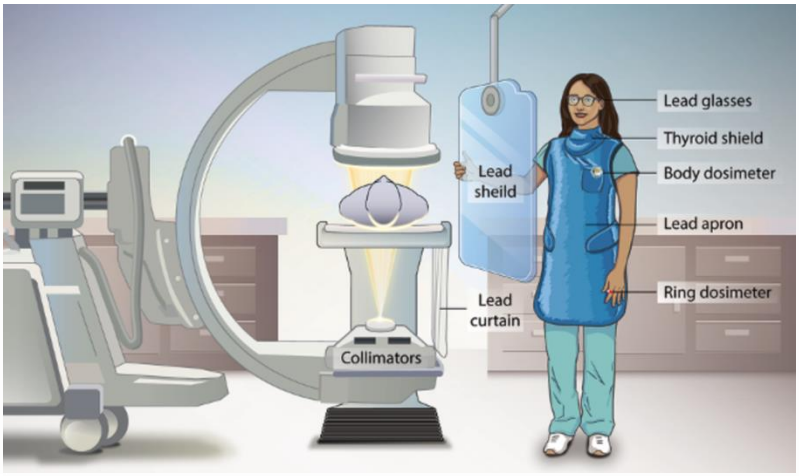
Table 4: Pulse fluoroscopy and effect on radiation dose



Distance: Radiation intensity is inversely proportional to the square of the distance from the source, such that doubling the distance reduces the doses fourfold. Increasing the distance from a source is more effective at reducing operator doses than reducing the exposure time.

Shielding: x-ray attenuation by lead is high due to its high density and atomic number. Lead aprons should have 0.25 – 0.5 mm of lead and should be worn at all times. Lead aprons are expected to attenuate at least 90% of an incident x-ray beam. Lead aprons can crack when folded improperly so they should be tested annually. Lead neck shield should be worn to reduce thyroid exposure and leaded glasses reduce eye lens exposure. (Figure 1) The table should have a lead curtain to protect the staff in the room. Leaded gloves may be used to minimize extremity doses

Figure 1: Devices available for operator and staff protection.



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Clinical Practice Strategies to Improve Patient Safety and Reduce Liability: Lessons from the Closed Claims Project

Name **Karen B. Domino, MD, MPH**
Seattle, Washington

Overview: This lecture will review strategies behind to improve patient safety and reduce liability, including methods to improve team communication, informed consent and patient engagement through shared decision-making, and best responses after a medical error or unexpected adverse outcome and improvements. Findings with illustrative case examples from the Anesthesia Closed Claims project will be provided.

Role of Communication in Patient Safety

Role of communication failure in patient injury. Communication between members of the health care team and between health care teams and their patients is critical to providing safe and effective medical care.[1] Communication failure ranked among the top three root causes of sentinel events reported to the Joint Commission in 2013-15.[2] Communication was the most common root cause of anesthesia-related sentinel events resulting in death or permanent loss of function reported to the Joint Commission in 2004-2015.[2] Communication failures frequently occur during surgery.[3-7] Most of this work has been performed by surgeons. Video-analysis of 10 high acuity surgical procedures identified 17 communication failures that compromised patient safety, with communication problems contributing to 7 (30).[4] A subset of these cases had communication failures occurring in every case with an average of one communication failure for every 8 minutes.[5] Failures were more common between medical disciplines than within the same disciplines.[5] Incident reports about communication failures within surgical teams found severe patient injury or death in 31% of reports.[6] Communication failures occurred in 13.5% of 444 surgical malpractice claims.[7]

Communication failures in patient injury: Findings from the Closed Claims Project. We studied communication failures associated with adverse patient outcomes focusing on anesthesia care. We analyzed malpractice claims in the Anesthesia Closed Claims database for claims for injuries occurring between 2004 to 2013.[8] Communication failures were classified according to definitions adapted from Lindgard et al.[3]: occasion, audience, purpose, or content. *Occasion (or timing*) failures were defined as problems in the situation or context of a communication event, mostly in that information should have been provided sooner. *Audience failures* were defined as gaps in the composition of the group engaged in communication, such as the absence or distraction of a key team member during the communication. *Purpose failures* were defined as communication events in which purpose was unclear, not achieved, or inappropriate, such as where healthcare professionals were inappropriate or disrespectful or unable to agree on a resolution to the issue. *Content failures* were defined as insufficient, inaccurate, or no information was transmitted. Examples of content failures included when there weren't any communication on the relevant topic, correction information provided but not reviewed or misinterpreted by the recipient, and inaccurate of ambiguous information provided. The timing, methods, and personnel involved in the communication failure were also analyzed.

Communication failure potentially contributed to injury in 43% (395) of 914 claims. Some claims had multiple failures resulting in a total of 453 failures. Agreement on whether failure occurred or not was 0.885 and whether a failure potentially led to the injury was 0.657. Failures were associated with emergency cases (21% in failure claims vs. 16% in no failure claims, $p = 0.04$), outpatients (34% vs. 26%, $p = 0.008$), and patient death (36% vs. 30%, $p = 0.03$). There was no association of failures with ASA physical status, gender, or obesity. The method of failed communication was most often verbal (62%). Most failures concerned intraoperative events (47%) or preoperative information/medical history (26%). The root cause of the failures was most often content failures (59%). The next most frequent root causes were audience (17%) and purpose (15%) failures. The anesthesia team was involved in 94% of the communication failures. The surgical team involved in 56%, nursing in 47%, and the patient/family in 22% of the communication failures.

Methods to improve communication: Team-training, standardized protocols, checklists, and hand-offs. Training and implementation of communication protocols have clear potential to improve anesthesia patient safety. *Team training* with protocols that emphasize interpersonal communications during crisis situations can have a positive impact, such as during massive hemorrhage, cardiac arrest, or other perioperative emergencies. Team training has been especially embraced in obstetrics and the emergency room. The high incidence of obstetric hemorrhage has prompted specific team training in this area that emphasizes the importance of early recognition, communication among team members, and defined – and practiced – treatment protocols. Training can take various forms. Team-training can improve healthcare processes and patient outcomes.[9] Team Strategies and Tools to Enhance Performance and Patient Safety (TeamSTEPPS, https://www.ahrq.gov/teamstepps/index.html) is one technique used to enhanced team communication. Crew resource management with ongoing simulation and practice has also been advocated to train OR and obstetric teams for emergencies.[10] One approach is to set up the simulation in the actual OR with no prior notice to the staff.[11] The Mobile Obstetrics Emergencies Simulator system, which has been aligned with TeamSTEPPS, demonstrates how simulation training and clinical drills performed in a facility's obstetric unit can improve team performance.[12]

Massive transfusion protocols. Another key component of communications and logistics during management of massive hemorrhage is the massive transfusion protocol (MTP), common at many university hospitals, obstetric units, and level 1 trauma centers.[13-15] This pre-arranged order set for the blood bank can be initiated at the point of care with a single phone call. The MTP provides for rapid delivery of blood products to the bedside, beginning with uncrossmatched and emergency-release products if necessary, and plans for continued delivery as the resuscitation progresses. Activation of the MTP is one component of the 'crisis checklist' that has been recommended for dealing with intraoperative emergencies. The protocols facilitate early replacement of clotting factors if coagulopathy is present or at high risk. In addition, activation of hemorrhage protocols enlist additional resources for resuscitation from hemorrhage, similar to rapid response teams.

MTPs are designed to facilitate the bedside clinician in replacing clotting factors early in resuscitation if coagulopathy is present or high-risk. A typical MTP calls for the blood bank to send 6 units of erythrocytes, 4 units of plasma and 1 apheresis pack of platelets to the OR as rapidly as possible, followed with similar 'transfusion packs' at regular intervals until the crisis is resolved.[15] The optimal ratio of erythrocytes, plasma and platelets is highly controversial, but current recommendations are to begin with empiric replacement of coagulation factors until hemorrhage has slowed sufficiently to allow for precise assessment of clotting function.[16]

Perioperative protocols/checklists. Perioperative protocols with checklists improve team communication and can improve patient safety. Implementation of a formal perioperative protocol with a checklist reduced surgical site infection, patient mortality, and unplanned return to the OR.[17,18] Theoretically, these protocols should reduce "never-events" such as wrong side surgery, cautery-induced fires, and medication errors associated with medication allergies. However, outcomes depend upon compliance to the protocol/checklist,[19] and in some locations, adoption of the perioperative protocol did not reduce surgical morbidity and mortality.[20] Implementation through principles of implementation science rather than a top-down imposed approach increased successful adherence to the protocol.[21]

Hand-offs. Hand-offs are defined as the transfer of information and responsibility for the care of a patient from one healthcare provider to another. In anesthesia, hand-offs occur during shift changes, breaks, and in transitions of care.[22] Information omissions, errors, and distractions are particularly common during postoperative hand-offs to the recovery room and ICU. There is some evidence that standardized hand-off processes, tools, or protocols can reduce communication errors and patient harm.[7,23,24] Barriers to effective hand-offs involve incomplete transfer of information, poor standardization, inconsistent teams, and other communication issues.[25] As a result of these gaps, standardized processes using checklists and protocols have been designed.[25,26] These hand-off protocols require all relevant team members to be present and completion of urgent clinical tasks prior to information transfer. Discussions during the hand-off are restricted to patient-specific discussions "sterile cockpit", with one person speaking at a time, and an opportunity to ask questions. Team training and simulation with feedback is recommended to improve the quality of hand-offs.

Role of Communication in Medical Liability

Factors leading to malpractice claims after an adverse outcome. Only a small proportion of adverse events, even after a medical error, lead to a malpractice claim. Brennan et al.[27] found that only 1 out of 8 adverse events associated with substandard care resulted in a malpractice claim. Several other studies found a poor correlation between medical negligence and malpractice claims.[28-30] The severity of patient disability, not the occurrence of a medical error or substandard care predicted payment to the plaintiff. These data suggest that there are many factors other than standard of care that drive medical malpractice after an unexpected adverse outcome.

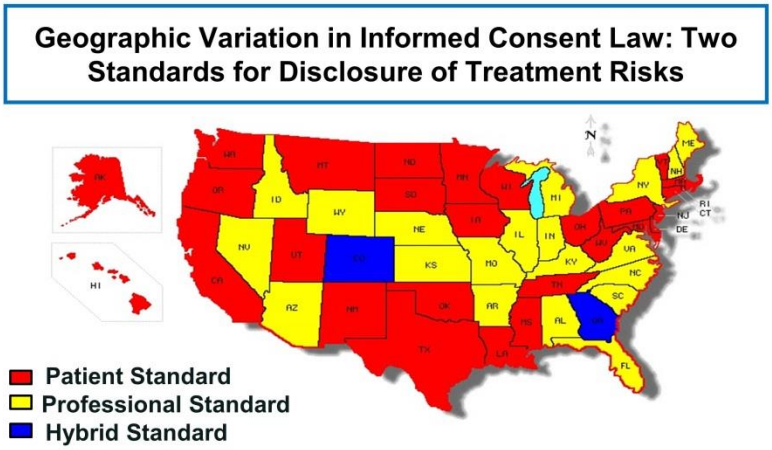
An important factor with a clear relationship with medical malpractice is a communication failure between physicians and patients. Avery et al.[31] found the top three reasons for why patients sue were communication issues (80%), arrogant physician attitudes (35%), and failures in communication (35%). Patients who sue are more likely to be unhappy with the interpersonal relationship with their physician than the outcome of their care.[32] Patients report greater satisfaction and a less likely to sue a primary care physician if they perceive the physician as communicative, caring, honest, personable, possessing a sense of humor, and apologetic, if appropriate.[33] In contrast, these personal characteristics were not predictive of lawsuits against surgeons. The authors suggested that a critical time for surgeon-patient communication was in the informed consent process, including the discussion about poor surgical outcomes.[33] A common reason that patients file a lawsuit is the need for an explanation or information that they perceive may have been purposely withheld.[32] Patient/family expectations for compensation and contingency fee arrangements with attorneys also drive malpractice claims.

Some physicians are sued more frequently than other physicians. A high-risk group of 2-5% physicians in a variety of specialties, including anesthesia and surgery, accounted for more than50% of malpractice claims in the state of Florida.[34] High malpractice-risk obstetricians possessed inadequate communication skills with patients and their families, but did not have more medical errors or substandard care.[35] In addition, physicians with a high frequency of malpractice claims often spent a shorter time with patients, exhibited communication problems and a lack of humanness.[36] Physicians with few malpractice claims showed greater use of facilitation, used more statements of orientation, laughed and used humor, had longer visits, but no differences in content discussed with patients.[36] Physicians who had been sued frequently were more often the focus of patient complaints by patients who did not sue.[34] Patient complaints concerning their hospital care were also non-uniform, with a larger share of complaints for care in hospital units with staff communication issues.[37]

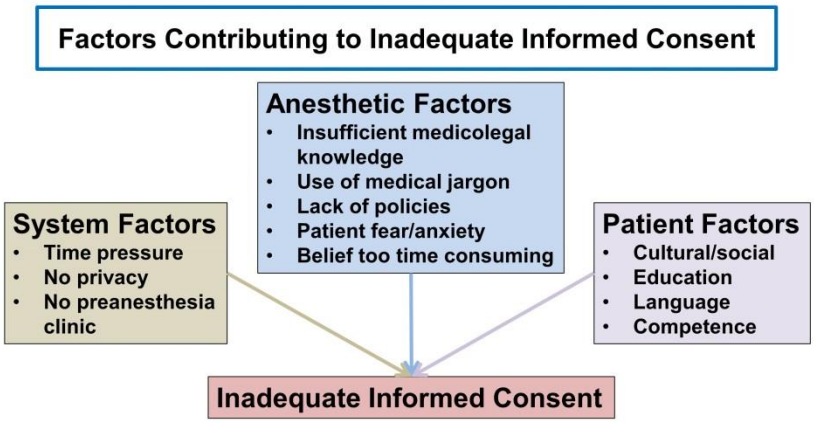
Role of communication in medical liability: Findings from the Closed Claims Project. Communication failures leading to increased liability were identified in 16% of 1132 anesthesia malpractice claims from injuries 2004-13.[38] The most common liability-related failures were inadequate or lack of informed consent (35%); inadequate, discrepant, or missing documentation (28%); poor witness factors (27%); and altered or falsified medical records (5%).[38] Liability-related claims were more commonly assessed as exhibiting substandard anesthesia care and payments on behalf of the anesthesiologist than claims without communication failures.[38] This highlights the importance of anesthesiologist communication in resolution of malpractice claims.

Informed consent. One of the most important times for communication with patients for both anesthesiologists and surgeons is during the informed consent discussion. Informed consent is an ethical obligation of the practice of medicine as well as a legal requirement. The informed consent discussion requires a thoughtful dialogue between physician and patient wherein sufficient information is imparted so that the patient can make an educated decision regarding medical treatments. In the U.S., the states are divided in the legal requirements for disclosure of risks and benefits. Some states adhere to a “reasonable patient standard” (i.e., what a reasonable patient would consider pertinent to making an informed decision), while others adhere to a “reasonable physician standard” (i.e., what another physician in the community would disclose under similar circumstances) (Fig. 1).[39] This geographic variation is important as jury verdicts for plaintiffs were significantly more frequent in states with a patient standard (27%) than in states with a professional standard (17%).[39] Multivariate analysis showed the odds of a jury verdict for a plaintiff to be twice as high in states with a patient standard (odds ratio = 2.15, 95% confidence interval = 1.32 to 3.50).[39]

Figure 1



In general, informed consent requires discussion of risks, benefits, and alternatives to treatment. Both common complications and significant "material" risks relative to the patient should be discussed. The informed consent discussion should be tailored to the patient's medical condition and specific procedure with specific risks documented in the medical record. Unfortunately, physicians often do not share the information patients need to make an informed decision. In practice, the informed consent discussion often discusses only plans and frequent minor risks, especially in anesthesia.[40] There are multiple reasons anesthesiologists provide limited discussion of risks in informed consent: production pressure and other systemic factors, anesthetic factors, and patient factors (Fig. 2).[41] A major reason some anesthesiologists fail to discuss material risks is that discussion of rare events will unduly increase patient anxiety. Some anesthesiologists believe the risks to be too low to warrant discussion with healthy patients. However, most patients are not unduly frightened by the discussion of risks.[42]



Shared Decision-Making. Shared decision-making is a mode of communication with patients to encourage engagement about treatments that have options, for which patient preferences, physician preferences, and professional opinion warrant consideration before a final treatment decision is made. Shared decision-making is appropriate when there is no medically "best" choice, as the best choice depends upon patient preferences, including individual weighing of risks, benefits, and alternatives. The option of regional anesthesia is often a preference-sensitive choice. Shared decision-making is supported by patient education tools to assist patients in making their choice. The content of decision aids includes an explanation of the choices, evidence-based presentation of risks and benefits along with probabilities and uncertainties about outcomes, and information to assist patients in evaluating the things that are most important to them in making their decisions (Table 1).

Shared decision-making improves patient knowledge and satisfaction, and patient engagement.[43] A higher proportion of patients had accurate risk perceptions with shared decision-making compared to standard informed consent. Shared decision-making also may decrease unnecessary interventions for a particular medical condition, resulting in less geographic variation of procedures, improved quality of health, and reduced health and reduced health care costs.[43] Patient complaints relating to risks and alternatives of treatment, seriousness of the condition, nature and uncertainty of the treatment (all informed consent-related complaints) are common and resource-intensive for risk management, and may lead to legal action.[44] Informed consent-related complaints can potentially be avoided by enhanced informed consent through shared decision-making.

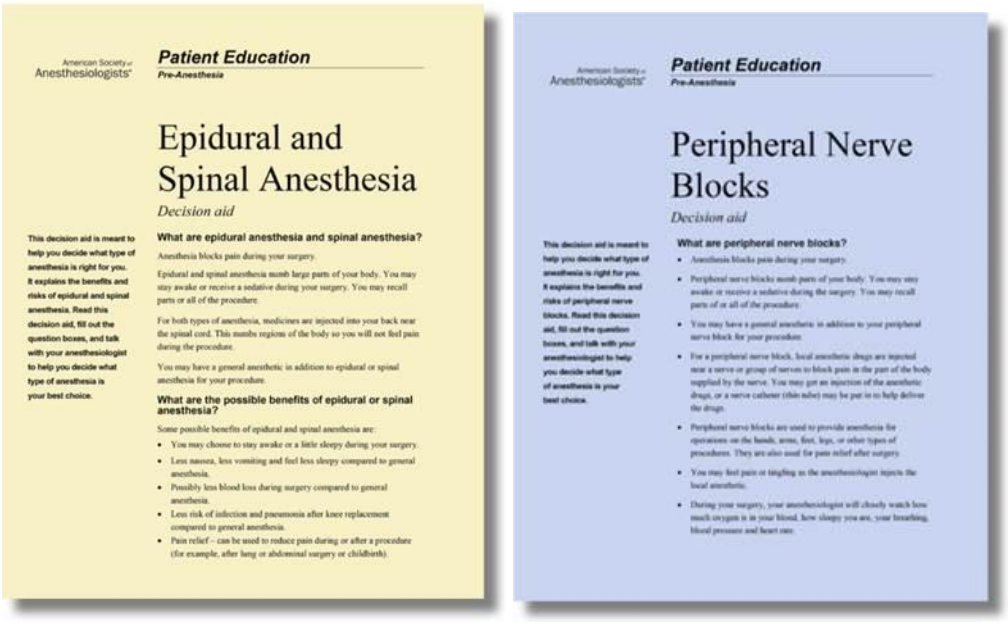
Table 1: Patient Decision Aid Content and Evaluation Criteria
1. Provide unbiased information about the options
Describe the options
Describe the risks and benefits
Describe the side effects
Include chances of positive and negative outcomes
2. Provide probabilities of the outcomes – unbiased
Compare probabilities using the same denominators
Describe uncertainty around the probabilities
Use multiple methods – words, numbers, diagrams
3. Include ways to clarify the patient's values – what is important in making the decision
Prompt patients to consider which benefits and risks are most important to them
Encourage patients to discuss their options with others and seek additional opinions
4. Use plain language
Grade 6-8 reading level
5. Use current scientific evidence
Include a reference section or appendix
Update the evidence on a regular schedule
6. Disclose funding source and potential conflicts of interest
Funding for development
Funding for distribution

Note: This list is an abbreviated version including only selected items from the full criteria developed by IPDAS. The full checklist is available at ***ipdas.ohri.ca/resources.html****.*

Shared decision-making may also confer legal protection for adverse outcomes when care is appropriate. Barry et al.[45] studied the judgments of mock jurors concerning several scenarios of informed consent concerning pros/cons of PSA testing in a hypothetical patient. This patient decided to not obtain a PSA after discussion with his physician, but developed invasive prostatic carcinoma a few years later. Only 17% judged the physician's care to be appropriate if the informed consent discussion was not documented in the medical record, whereas if consent was documented in the medical record, 65% believed care to be appropriate. If shown a decision aid in video format concerning PSA testing, 96% of the mock jurors judged the standard of care to be met. In Washington State, the legislature incorporated medical legal protections if shared decision-making with use of patient decision aids is used in the informed consent discussion.[46]

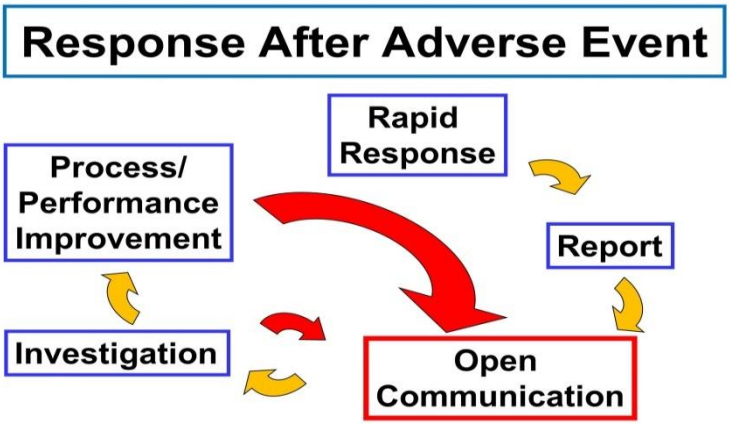
Shared decision-making aids for anesthesia. The ASA Committee on Professional Liability and Committee on Patient Safety developed shared decision-making aids for regional anesthesia (neuraxial block and peripheral nerve blocks, Fig. 3). These decision aids are written at an 8th grade level and incorporate evidence concerning regional block risks and benefits.[47] The decision aids were tested with patients in a pre-anesthesia clinic. They were shown to increase knowledge about regional anesthesia, but did not affect patient anxiety and were well received by patients.[48] Patient engagement increased, and more patients discussed anesthesia options if they were given a decision aid before their visit, compared to patients who did not receive decision aids.[48] The decision aids are posted on the ASA website site and are available to adapt into practice (www.asahq.org/resources/resoucesfrom-asa-committees#Patient_Safety). Other decision aids for monitored anesthesia care, general anesthesia, end-of-life care, among others, are in various stages of development.

Figure 3



Communication after an unexpected adverse outcome.
Communication with a patient/patient's family takes special significance after an unexpected adverse outcome. Anesthesiologists face unique challenges in this communication due to the lack of a pre-existing relationship.[49] In most cases, anesthesiologists meet the patient shortly before administering the anesthetic, in some settings, they may not meet any of the patient's family members. In addition, the anesthesiologist acts as a member of the surgical team, which poses challenges related to the timing of the discussion with the patient's family and coordination with other members of the surgical team.[49] The anesthesiologist may be invovled in patient care while the surgeon may initially discuss the events with the family and doesn't know what the surgeon described to the family. Communication after an unexpected adverse event should be performed in a quiet room with the pager and phone off. The anesthesiologist should accompany the surgeon to the discussion with the family. Recommendations concerning how to best handle this situation include: 1) provide an empathetic "warning shot" such as I'm sorry but I have bad news to tell you, 2) non-verbal communication is key, 3) lean forward and maintain eye contact, 4) don't act inpatient or uninterested, 5) pay attention to subtle cues, 6) paraphrase the family's questions in the discussion and allow time for questions, and 7) provide an expression of empathy or regret over the adverse outcome.

In situations of a severe unexpected severe adverse event or a medical error, formal disclosure protocols, including a formal apology, if indicated, are commonly used in the US.[50] While the anesthesiologist is involved in the disclosure particularly immediately after the event , professional risk managers often lead these discussions with patients and patient families. The formalized response after the adverse event involves a rapid response with the family, an initial formal report, ongoing open communication with the family (generally lead by the same one individual); investigation into the event, including root cause analysis; continued communication with paitent/family; process and performance improvement; and a formal apology, if indicated (Fig. 4). The key content to be disclosed to the patient identified by the National Quality Forum includes facts about the event, including presence of error or system failure; error or system failure.[50] The institutional requiremnets include integration of disclosure, patient safety, and risk management activities; development of a disclosure system, involving disclosure education; 24-7 dislosure coaching, and emotional support for healthcare workers, patients, and families; and use of performance improvement tools to track and enhance disclosure.[50,51]



Several states (Nevada, Florida, New Jersey, Pennsylvania, Oregon, Vermont, and California) have mandated that institutions disclose serious unanticipated outcomes to patients/families.[50] At least 34 states have passed "apology" laws that protect specific information contained in disclosures, most commonly apologies or other expressions of regret. Two-thirds of the states only protect the apology or expression of regret, not the information related to causality ("our care caused your injury") or fault ("this should not have happened").[50, 52] Also attorneys pick and chose what claims they wish to pursue and information from disclosure can be helpful to them. Thus, while apology laws are useful policy endorsements of disclosure, they are unlikely to influence disclosure behavior in most states.

Disclosure after an adverse event has been shown to reduce litigation costs in a number of settings, including the VAH, University of Michigan, University of Illinois in Chicago, and the COPIC insurance program in Colorado.[50] Disclosure may not prevent a lawsuit especially in the context of a medical error or substandard care. Since disclosure is often followed by an offer of compensation for the adverse outcome' This process reduces litigation costs in the situation of a medical error or substandard care. An early settlement reduces costs by reducing costs of review by expert witnesses, depostions by experts and involved personnel, and excess attorney investigation.

Disclosure is also thought to reduce unneccessary litigation in the case of appropriate care as there is no longer a need to file a malpractice claim to find out the cause of the unexpected outcome.

Summary: Communication failures are an important cause of patient injury. Team-training, standardized protocols, checklists, and hand-off protocols reduce harm and improve perioperative patient safety. Communication with patients/families is also important. Communication during the informed consent discussion and after an unexpected adverse outcome is particularly important for anesthesiologists. Shared decision-making tools improve patient knowledge and engagement. The ASA currently offers evidence-based decision-making aids for regional anesthesia (epidural/spinal anesthesia and peripheral nerve blocks). Disclosure after an unexpected adverse event is common in the US and appears to reduce overall malpractice costs.

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ANESTHESIOLOGY 2017
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Perioperative Management of Patients With Left Ventricular Assist Devices Undergoing Non-cardiac Surgery

Michael F. O'Connor MD FCCM **Chicago, IL**

Left Ventricular Assist Devices and other mechanical circulatory assist devices are being increasingly used in the management of patients with heart failure. At many centers, and in many major metropolitan areas, there are now a large number of patients with such devices. Their care is no longer considered exotic, and in many hospitals, physicians are expected to be able to provide elective as well as urgent and emergent care for these patients.

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What you need to know:

- Anatomy of these devices?
- Indications for these devices?
- How do these devices change a patient's physiology?
- Complications of implanting these devices?
- Clinical Implications of all of this?

What is the anatomy of these devices?

The vast majority of the devices implanted in the past 5 years have been Heartmate 2 and Heartware LVADS. It is likely that the Heartmate 3 will reduce the numbers of both of these devices implanted in the next several years. A variety of newer, smaller devices are under development. If these devices come to market, it is almost certain that the implantation of these devices will increase dramatically, and that they will be inserted into patients earlier in their evolution of heart failure. Among the "pulsatile" devices, the Total Artificial Hart has enjoyed an increase in use at several centers over the past few years.

Non-pulsatile = Continuous Flow

- Heartmate 2 (>22,000 May 2016)
- *Heartware* (>10,000 May 2016)
- *Heartmate 3*
- *MVAD*

- *Heart Assist 5*
- *Duraheart*
- *Incor*
- *VentrAssist*
- *MiTiHeart*
- ***Others……***

Pulsatile

- Thoratec PVAD IVAD (>3000)
- Syncardia Total Artificial heart

Who gets these Devices?

Long-term devices (listed above) are most appropriately inserted into patients with the following diagnoses:

Ischemic DCM

Non-Ischemic DCM

- Often ischemic
- Peri-partum CM
- EtOH (admitted or not)
- Auto-immune

- Not yet for muscular dystrophy, or Marfan's

Purpose?

The use of mechanical circulatory assist devices to rescue patients in crisis has increased dramatically over the past several years. This has in turn created new paths of hospital care for patients who would previously died of cardiogenic shock. Bridge-to-Recovery leads to Bridge-to-Decision, Bridge-to-Destination therapy, or Bridge-to-Nowhere (Sladen 2017). Patients who receive short-term devices whilst in crisis are often advanced to long-term devices if they have a favorable recovery. In some instances, patients can recover sufficiently that they may no longer require any mechanical support. Some of the devices employed for short-term support (e.g. Centrimag) are not regarded as appropriate for longer term use, but are still often used for months. In many instances, VA ECMO for a patient in crisis eventually leads to a long-term LVAD.

Short term (typically VA ECMO or Centrimag LVAD/RVAD)

- Bridge-to-Recovery (e.g. cardiac arrest or severe cardiogenic shock)
- Bridge-to-Evaluation/Decision (e.g. poor recovery from acute event)
- Bridge-to-Bridge (e.g. no recovery of LV function after cardiogenic shock→ longer term device)

Long-Term

Bridge-to-Transplant

- Recipient is believed to be a good candidate for heart transplant
- Once upon a time, most patients listed for heart failure died awaiting an organ.
- ~70 % survive to transplant
- ***drive line infections and bleeding during transplant have increased interest in alternatives***

Destination

- Recipient is ineligible for heart transplant
- Dramatic improvement in functional status among those who do not suffer major complications
- 1 year survival has dramatically improved over the past several years

How do these devices change physiology?

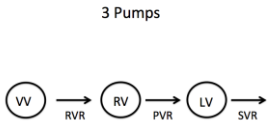
- Pulse → minimal pulse or pulseless (pulsation that is present comes from ventricular contraction augmentation of inflow into device)
- Anticoagulation heparin → warfarin - exact protocols and targets in evolution (e.g. PREVENT registry)
- Acquired vWF disease (perhaps much less of a problem with the HM3 (see Uriel 2017))

Pulsatility Index (PI)

- Occurs with *all* continuous flow devices (but not pulsatile), but is not reported by all manufacturers.
- Index of augmentation of forward flow from cyclical increased *inflow* by LV contraction
- Higher Pump speeds (RPM) →decreased PI
- Increased Contractility → increased PI
- Decreased Contractility → decreased PI
- Increased Circulatory volume →increased PI
- Decreased Circulatory volume → decreased PI

PI = [(flow max – flow min)/ flow average] x10

Circulatory Physiology



Left:

- MAP is both created by the LVAD and the pressure against which it pumps
- Goal MAP = 70-80 mmHg (Watts = Heat)
- MAP >90 mmHg is a recognized risk over long-term for Intra-cranial bleed
- Aortic valve continuously subjected to high pressures and unfavorable geometry →AI
- High Pump speeds suck septum into inflow tract (↓likely better than ↑) = Suction Event

Right:

- RV outflow is LVAD inflow
- MAP perfuses the RV (PA HTN)
- PVR still matters
- Fontan Flow is possible in patients with a normal PVR

Venous:

- Venous return matters → intravascular volume matters
- Venous tone matters → use vasoconstrictors as usual for vasoplegic shock

Complications – why YOU will see them:

Patients with LVADs are admitted to the hospital with either complications of their heart failure, their co-morbidities, or from their device.

- Bleeding 44%
- Infection 46%
- Respiratory Failure 20%
- Renal Failure 10%
- Stroke 6.5%
- Liver Failure 6.5%
- Hemolysis 3%
- Venous Thromboembolism 6.5%
- RV Failure 15%
- Depression 8%
- *Acquired AI*
- *LVAD thrombosis (8.5% incidence with 48% mortality)*
- *Device Failure*

Why do these patients come to the ICU/OR?

Increasingly, patients with LVADs are regarded as appropriate for any intervention or procedure that is otherwise indicated in them (Stone 2015).

- EGD/colonoscopy/DBE for GI bleeding (by far the most common procedures for LVADs)
- Drain pus – drive line, chest wall, pleural
- Drainage of hematoma – intracranial, other
- Cancer operations – esp. abdominal operations/obstructions
- Laparotomy/laparoscopy
- Sternal debridement
- VATS/decortication
- *Thoracic procedures*
- *Aortic valve operations*
- *LVAD replacement*

Clinical Considerations

- Is the stomach full? Blood?
- Hold or reverse anticoagulation as required (Acquired vWF) FFP preferable to rFVII or PPC
- Previous trach → may require smaller tube
- Vasculopath?
- Sildenafil, milrinone, midodrine = tenuous RV
- Patients with limited RV function kept very dry
- Wall Power > Battery Power (console calculates flow)
- Goal MAP = 70-80mm Hg (RV perfusion)
- Spontaneous ventilation > Mechanical ventilation
- Least positive pressure ventilation is better (Small TV, low rate)
- AICD/pacemaker still requires evaluation and a plan for management

Monitoring

- Capnography detects presence of circulation
- Mission Impossible = Assessment of volume status. Pulsatility Index (PI) is most reliable. Low threshold for TEE to assess LV volumes.
- NIBP & Pulse will generally work if the patient is not hypotensive or hypovolemic
- Bleeding can be insidious → frequent ABGs (GI bleed)
- When in doubt, measure lactate levels
- Central Line if vasoactives might be required (?PICC?)
- Sepsis→ usual RX with Norepi or Vaso
- Echo/TEE ?

Crisis Management

There are now published protocols about how to evaluate and manage patients with LVADs who are found unresponsive (see Yuzefpolskaya 2015). Non-perfusing rhythms can cause a circulatory crisis in a patient with an LVAD, particularly those whose PVR is elevated and are thus unlikely to have Fontan flow.

- BEWARE the RV! RV outflow is LVAD inflow
  - Maintain the circulating volume (replace blood, bodily fluids, insensible loss)
  - Maintain Perfusion – Neo, Vaso, Norepi (almost never lower flow)
  - Maintain Contractility – Dobut
  - Worst case scenario – iNO/ VA ECMO
- Remember – MAP perfuses the RV
- Rhythm matters – for the RV
- CPR/ACLS is for the RV – Do It!!!

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ANESTHESIOLOGY 2017
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Post Dural Puncture Headache and Epidural Blood Patch

Barbara M. Scavone, MD **Chicago, IL**

Introduction

Post dural puncture headache (PDPH) is one of the most common adverse events to occur after neuraxial anesthetic procedures. Most of the data concerning both PDPH and epidural blood patch (EBP) comes from the obstetric anesthesia literature, although a smaller amount derives from the pain and other anesthesia literature.

Incidence, clinical features, and etiology

Meta-analysis reveals that: The incidence of accidental dural puncture (ADP) with a large bore needle during epidural anesthetic procedures is approximately 1-2%, although the range varies across different reports. In obstetric patients, PDPH follows 50-60% of ADPs. Of those patients with PDPH, 50-60% require EBP. PDPH occurs in the absence of a recognized ADP in fewer than 1% of patients (1). A typical PDPH is positional, such that headache worsens in the upright position, and abates (although perhaps not completely) when the patient assumes the recumbent position. Headache may be accompanied by neck ache and back pain, visual symptoms such as photophobia and blurred or double vision, auditory disturbances including decreased hearing acuity and tinnitus, and even cranial and upper cervical nerve dysfunction. Onset is usually within 1-2 days, and duration, 7-10 days in the obstetric population (1). Onset may lag and duration may be shorter in general surgical patients. The differential diagnosis of headache in postpartum patients includes states specific to pregnancy such as preeclampsia, venous thrombosis, and intracerebral bleeds, as well as more generic causes of headache such as tension headache; migraine may recur in the postpartum period also (2). Diagnostic neuro-imaging should be considered for postpartum patients whose headache is accompanied by focal neurologic signs or lack of response to treatment, as these can be signs of intracranial pathology (2).

Headache occurs due to leakage of cerebrospinal fluid (CSF); however correlation between headache symptoms and degree of leak/intracranial hypotension is incomplete. Some patients with small lumbar leaks develop headache, whereas some with large leaks do not report any symptoms (3). Similarly, a proportion of patients with severely depleted intracranial CSF volume may remain asymptomatic, while some with only mild CSF decreases develop severe headaches (4). When the brain loses its CSF cushion, downward displacement of the cranial contents may occur, putting traction on pain-sensitive meningeal structures. Furthermore, reflex cerebral vasodilation occurs in response to intracranial hypotension and pain-sensitive perivascular stretch receptors may contribute to headache symptoms (5).

Risk factors for PDPH

Patient-related factors. Young age and female gender are risk factors for development of PDPH after dural puncture (6). Whether pregnancy itself is an independent risk factor remains unclear. Obesity predisposes to ADP (7). The effect of obesity on headache rate once ADP occurs is less clear because retrospective studies demonstrate conflicting effects (8, 9, 10, 11). Obese patients may have a better response to epidural blood patch (EBP) versus non-obese patients (12).

Obstetric-related factors. Patients who have vaginal delivery are more likely to develop headache after ADP than those who undergo cesarean delivery (13). Performance of Valsalva maneuvers during pushing may cause extrusion of CSF, as headache rate is proportional to pushing time (14). Furthermore, patients often receive spinal morphine after cesarean delivery, which decreases headache pain (15).

Technique-related factors. Headache rates increase after puncture with large-gauge versus small-gauge needles, and beveled/cutting versus pencil point/non-cutting needles (6,16). One group of authors demonstrated that inserting an epidural needle with the bevel parallel to, rather than perpendicular to, the longitudinal axis of the spinal canal,

decreased headache rate (17). They recommended holding the bevel parallel to the long axis to identify the epidural space, and then rotating the needle within the space once it had been identified, to decrease the risk of the catheter veering off to one side, resulting in unilateral blockade. Others questioned the utility of this practice, demonstrating that it was not necessary for satisfactory analgesia to rotate the needle before threading the catheter into the epidural space (18). Rotation of the needle within the epidural space may increase ADP occurrence.

The effect of loss of resistance (LOR) medium used during epidural space identification on headache development remains unclear. One author demonstrated higher headache rates in pain patients after LOR to air versus saline (19). However, the air-related headaches had faster onset and shorter duration than the saline-related headaches, and therefore may have been due to temporary pneumocephalus that resulted from injection of air into the intrathecal space during LOR. Practitioners should aim to inject the smallest amount of air possible into the epidural space during LOR in order to minimize the development of pneumocephalus should ADP take place.

Once ADP has occurred, one may elect to thread a catheter into the intrathecal space for continuous spinal anesthesia, or to withdraw the epidural needle, and re-site it into the epidural space at a different intervertebral level. Some have theorized that intrathecal catheter insertion causes inflammation near the dural tear, speeds healing, and decreases headache risk. Retrospective and other uncontrolled studies addressing this possibility are confounded, and therefore yield conflicting results, some demonstrating lower headache rates with intrathecal versus epidural catheterization and some showing no effect. Two randomized controlled trials investigating the relationship of intrathecal catheterization and PDPH risk exist. Norris used a quazi-randomization technique to assign parturients to receive intrathecal versus epidural anesthesia after ADP, and showed no difference in headache rate or severity or in need for EBP (20). In the definitive study, Russel et al randomized obstetric patients to receive intrathecal versus epidural catheterization after ADP (21). Intrathecal catheters were left in place for 24 hours post delivery to maximize the pro-inflammatory effect. Headache occurred at equal rates in both groups, as did performance of EBP. The weight of the evidence therefore does not support the notion that intrathecal catheterization decreases headache risk after ADP. A meta-analysis that drew the opposite conclusion included both randomized and non-randomized trials, and was therefore flawed (22).

Issues other than the effect on headache rate should be considered after ADP. In the Russell study, patients in the epidural group suffered more complications than those in the continuous spinal group, such as repeat ADP and failure to establish blockade (21). Therefore, the authors recommended intrathecal catheterization after ADP despite its lack of efficacy regarding headache prevention. Some caution is warranted, however, because high spinal levels may result if local anesthetic doses intended for the epidural space are accidentally administered intrathecally. High spinal level can also result through an epidural catheter after a previous ADP because local anesthetics may translocate across the large-diameter hole in the dura, particularly during bolus administration for cesarean delivery. Similarly, epidural-administered hydrophilic opioids may traverse across the dural tear, so epidural morphine is contraindicated after a prior ADP. (Lipophilic opioids such as fentanyl traverse the dura quite freely and so the presence of the tear does not affect their dosing.)

Prophylaxis and treatment

Conservative therapy. Bedrest after ADP does not prevent PDPH, and inactivity remains inadvisable for postpartum patients due to their risk for deep venous thrombosis. One should maintain euvolemia as dehydration results in decreased CSF production; excessive hydration, however, does not promote excess CSF production. Abdominal binders may favorably affect pressure gradients across the dural tear and decrease PDPH after ADP; unfortunately, they are not well-tolerated by most patients and are not popularly used. Practitioners commonly prescribe analgesics, particularly those combination pills that include butalbital and caffeine. Caffeine, by way of its vasoconstriction properties, may decrease headache symptoms (23), but its effect is modest and transient, and so while clinicians may encourage patients to consume extra caffeine for mild or moderate headaches, severe headaches usually warrant other treatments. Also, caffeine has a prolonged half-life in postpartum patients, and accumulation may occur after repeated dosing or infusion (24). Furthermore, reports of seizure and arrhythmia during caffeine infusion exist (25,26).

Alternative therapies. One small trial investigating utility of sumatriptan in this clinical setting produced disappointing results (27). ACTH analogs increase aldosterone levels, and some theorize that the resultant salt and water retention may lead to increased CSF production, but studies investigating their usefulness have yielded conflicting results. One investigation indicated ACTH analogs were appropriate for PDPH prophylaxis (28), but another showed no effect of ACTH analogs on established PDPH (29). Clinicians have administered sphenopalatine ganglion blocks for PDPH but prolonged effect has not been demonstrated. Further study is needed.

Epidural blood patch. EBP remains the treatment of choice for severe PDPH (30). Injection of blood into the epidural space quickly produces a tamponade effect on the intrathecal sac, increasing epidural and intrathecal pressures in both the lumbar and intracranial spaces, restoring intracranial pressure, and relieving adenosine-mediated vasodilation (31,32,33,34). In addition, clot adheres to the dura after several hours, presumably decreasing leak and promoting healing (33). MRI studies indicate that approximately 15-20 mL blood is sufficient for spread and tamponade of the sac (31). A randomized controlled trial conducted by Paech et al compared 15 versus 20 versus 30 mL blood for EBP (35). All volumes of blood were similarly effective for treatment of headache symptoms; however, the area under the time-pain curve over 48 hours was higher in patients given 15 mL of blood compared to patients in the other groups, and the authors therefore recommended the use of 20 mL blood for EBP. One group reported 100% successful response to patch when they routinely administered as much as the patient could tolerate, up to 30 mL (36).

Retrospective audits reveal that 88-100% of obstetric patients with PDPH after ADP experience some degree of relief after EBP; however, some patients have only partial or temporary relief, and symptoms often return after a few days (36,37,38). Up to 31% of patients may require repeat patching (35). Although EBP lacks perfect efficacy, complete lack of any effect at all should spur the clinician to question the diagnosis of PDPH.

It remains unclear how timing effects EBP efficacy. Studies purporting to show decreased efficacy when patches are administered within less than 24 to 48 hours of puncture are difficult to interpret because they include a mixture of patients (male, female, obstetric, non-obstetric) and needle sizes and types used for puncture (12,39,40). It is just as likely that patients at high risk (e.g., obstetric patients delivering vaginally, suffering large-bore dural punctures) experience severe symptoms early after puncture, and are therefore patched earlier than others, and are also more likely to need repeat patching (36). While it is certainly reasonable to offer a patient experiencing mild or moderate symptoms a trial of conservative therapy, one should not hesitate to administer EBP to patients with severe symptoms within a day of puncture. Such patients should be made aware of the possibility of repeat patch requirement. A more positive approach to early patching may result in less pain over time and a better patient experience (41).

Prophylactic EBP can be performed through the epidural catheter before it is pulled out after delivery. Two randomized controlled trials stand at odds regarding the efficacy of prophylactic EBP. One demonstrated no difference in headache incidence, peak pain scores, or need for therapeutic EBP after prophylactic EBP compared to a shame patch, although those who received the prophylactic patch had shorter duration of headache (13). A second did show fewer headaches and therapeutic EBPs performed in those patients randomized to receive prophylactic EBP versus nothing (42); however, this study has been criticized because the treating physician was not blinded to patient group and treatment was not standardized, leading to possible bias (43). Considering these two studies together, it is likely that prophylactic EBP provides some benefit in high risk patients, although probably not a dramatic one (43).

Backache follows epidural blood patch in 85% of patients (35). Discomfort is usually mild, although occasionally can be more severe or be associated with radicular pain. It may be advisable to limit injectate volume, particularly if the patient feels pain or radicular symptoms during the procedure. Non-steroidal anti-inflammatory agents often provide relief. Rarely, more severe complications follow EBP, including deterioration of mental status and seizures when EBP is performed for headache other than PDPH (44), neurologic deficits after accidental subdural injection (45), and arachnoiditis (46).

Scope of the problem

Postpartum PDPH increases length of hospital stay, increases hospital and emergency department visits after discharge, and interferes with activities of daily living, including childcare (47). The sixth cranial nerve may become stretched during downward brain displacement, causing nerve injury and subsequent double vision (48). Often, PDPH responds to EBP treatment, but the diplopia persists for many months during myelin regeneration, or in rare instances, is even permanent (48). Sixth cranial nerve palsy is an indication for immediate emergency EBP to affect relief of nerve ischemia. Rarely, subdural hematoma follows PDPH, as bridging veins are stretched, and subjected to increased transmural pressures (49). EBP may limit hematoma extension.

There may exist longer term consequences to ADP than has previously been thought. Investigators who compared parturients who suffered ADP to a matched cohort who had not, revealed that patients in the ADP group had increased rates of headache and backache approximately 12 to 24 months post-delivery (50,51). EBP appeared to provide some protective effect against these long-term symptoms; however, the lower headache and backache rates in patients who had received EBP versus those who had not, did not reach statistical significance, possibly because the study was underpowered for this outcome (50).

Conclusions

ADP and PDPH continue to pose vexing problems for the anesthesiologist. EBP remains the mainstay of therapy for severe headaches.

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Pediatric Patients With Congenital Heart Disease for Non-Cardiac Emergency Cases

Nina Deutsch, MD **Washington, DC**

With improvements in the management of children with congenital heart disease, the size of this patient population continues to grow. This has resulted in a greater number of these patients undergoing anesthesia for non-cardiac surgery. However, multiple studies have demonstrated that they are at significantly increased risk of anesthetic complications.[1-6] In addition, the need for surgery to occur in an emergent manner further complicates the situation. This review will discuss a structured approach to children with congenital heart disease, review which pediatric patients are at increased risk for cardiac arrest under anesthesia, and describe appropriate anesthetic management of these patients.

An Approach to Congenital Heart Disease

For all patients with congenital heart disease, it is important to understand the precise anatomy as well as what pressures impact the direction and amount of blood flow. Blood flow will follow the path of least resistance, which is almost always from left (systemic) to right (pulmonary). However, the amount of flow will depend on how restrictive the shunt is. In an unrestrictive shunt, the flow will depend on the relative vascular resistances of the two vascular beds and can result in a significant amount of blood flow into the pulmonary system. However, in a restrictive shunt, some level of stenosis will be the point of maximal resistance and limit the amount of shunting that can occur.

Ultimately, the goal is to determine the relative pulmonary (Qp) to systemic (Qs) blood flow in order to establish how well "balanced" the circulation is (Table 1). The Qp:Qs ratio will most often be determined in the cardiac catheterization lab through the use of the Fick Principle. However, this data is not always attainable in an emergency situation or readily available on all patients. Therefore, when a patient is on room air (and without significant lung disease), the Qp:Qs ratio can be estimated using arterial oxygen saturation (SpO_2). In a patient with no level of shunting, the Qp:Qs ratio should be equal to 1. In a fully mixing lesion, in which the blood going to the aorta is a mixture of blood from both the systemic and pulmonary venous return (i.e. single ventricle physiology), the SpO_2 on room air should be 75-85% if the Qp:Qs is 1.

Qp:Qs ratio	Relative Blood Flow	Clinical Picture
< 1	Right to Left Shunt	Cyanosis
1-1.5	Minimal Left to Right Shunt	Asymptomatic, murmur, normal ECG
1.5-3	Moderate Left to Right Shunt	+/- symptoms; mild CHF
3-5	Large Left to Right Shunt	Very symptomatic with CHF; failure to thrive

In the preoperative period, it is extremely important to determine and understand the precise anatomy of the patient's congenital heart disease. The vast majority of patients will have an echocardiogram in their recent past that will be key to review. The presence of shunts, conduits, and valve gradients should be noted. Importantly, the heart function should also be determined. The patient's previous cardiac surgeries will need to be reviewed as well in order to determine which palliative or corrective procedures have already been undertaken.

Once this data is reviewed, it is important to validate that this data correlates with the patient's vital signs and SpO_2. If there is a significant discrepancy, is there something else that explains this? For instance, if a patient with single ventricle physiology awaiting their stage I palliative cardiac surgery has a significantly lower saturation than expected, there could be several explanations for this, including an intrinsic pulmonary issue (pneumonia, pulmonary hypertension) or increased right-to-left shunting across a fenestration. On the other hand, if the SpO_2 is significantly higher than expected, there could be pulmonary over-circulation at the expense of systemic circulation,

which can lead to a metabolic acidosis from poor perfusion. In each of these scenarios, one must then determine what effect, either positive or negative, the administration of oxygen will have.

Finally, it is important to consider what impact the proposed surgery and anesthetic will have on the patient's physiology. As in all patients, prolonged NPO times, dehydration, anesthetic agents, and systemic infectious disease will cause a decrease in systemic vascular resistance (SVR) while pain, hypoxia, hypercarbia and atelectasis can increase pulmonary vascular resistance (PVR). The relative ratio of pulmonary to systemic blood flow in the presence of shunts can change in these scenarios and potentially complicate the perioperative management of the patient. In emergency surgery situations, there is often not an option to delay surgery in order to fully optimize the patient. Therefore, the anesthetic plan needs to monitor, treat and mitigate these issues.

Pediatric Cardiac Patients at Increased Risk

In 1994, the Pediatric Perioperative Cardiac Arrest (POCA) Registry, a multi-institutional database, was formed to determine the cause of cardiac arrest in anesthetized children.[7] While initial reports from the registry showed significant medication-related morbidity, the causes of arrest have evolved over time with improvements in anesthetic agents. Hypovolemia, transfusion-related hyperkalemia, and respiratory events accounted for the majority of arrests in the latest report from 2010. However, 34% of cardiac arrests occurred in children with congenital heart disease. Of those, over 50% occurred in children with single ventricle physiology, shunting lesions, or obstructive lesions, especially aortic stenosis. Seventy-five percent of deaths were also accounted for in the following three groups: single ventricles, cardiomyopathy, and aortic stenosis. Furthermore, these arrests were more likely to occur in the general operating rooms rather than the cardiac operating room or the catheterization lab.[1] Patients with pulmonary hypertension also are at increased perioperative risk.[3]

Compared to children with low RACHS (Risk Adjustment in Congenital Heart Surgery) scores, those in higher categories 4-6 are more likely to have non-cardiac surgeries.[8] Patients with single ventricle physiology, in particular, undergo various types of non-cardiac surgery, most commonly placement of peripheral or central venous lines, insertion of gastrocutaneous tubes (percutaneous or laparoscopic), and airway procedures.[6] In this subset of patients, anesthesia-related complications typically range between 11-15% but are as high as 31% in older Fontan patients.[6, 9-10]

Due to the increased risk in these patient populations, several centers have stratified patients into risk categories based on age and/or complexity of disease to help standardize preoperative evaluation as well as determine whether sub-specialized cardiac anesthesiologists are needed to care for the patients in the perioperative period.[5, 11-12] While specific criteria may vary between centers, some stratification should be developed based on the comfort level and training of each group's anesthesiologists. In emergency situations, however, there may not be an option to wait for a sub-specialty team before proceeding, and it is imperative that the general anesthesiologist understands the complexity of these patients' care and applies that knowledge in his/her care until the sub-specialty team arrives.

General Principles of Perioperative Management in Patients with Congenital Heart Disease

Preoperative: As in all patients for surgery, a thorough preoperative evaluation is imperative to best care for patients with congenital heart disease in the perioperative period. While this can be difficult in an emergency situation, at a minimum, the echocardiogram and any cardiology notes that are available should be reviewed (as described above). Again, the clinical picture of the patient should match the data that these studies provide, and if there is a discrepancy, the cause of this should be determined. Consultation with the team managing the patient preoperatively can be extremely helpful in shedding light on the patient's current findings and is strongly encouraged.

As complete a review of systems as possible should be done during initial evaluation of the patient. Many patients with cardiac disease can also have significant co-morbidities, such as pulmonary disease, airway abnormalities, liver or kidney dysfunction, and neurologic delays. These may affect the anesthetic in numerous ways, including drug uptake and metabolism, the ease of intubation, and ventilation. Review of medications is also imperative. Many patients will be on medication for anti-coagulation at baseline. This needs to be taken into account to determine if it is necessary (or possible) to reverse its effects prior to proceeding and thereby reduce intraoperative blood loss. Furthermore, in emergency situations, medications such as dopamine, epinephrine, or vasopressin may be infusing due to hemodynamic instability. If not started already, induction of anesthesia and the

surgery itself may warrant the need for an inotrope, so emergency medications at appropriate concentrations should be available for immediate use.

The effects of a prolonged NPO time need to be considered. In general, patients in the higher risk groups (single ventricle, pulmonary hypertension, LVOT obstruction) should have intravenous fluids to prevent significant dehydration. As time allows, any fluid deficits should be corrected, beginning preoperatively and then continuing into the intraoperative period. Maintenance fluids can then be initiated. In younger age groups, maintenance fluids should include dextrose at an appropriate concentration for the patient's age.

Beyond the standard ASA monitors, the need for additional invasive monitoring such as an arterial line or central venous catheter will depend on the patient's underlying cardiac disease, their functional status, and the nature of the surgery. In many shorter and less invasive procedures, no additional monitors are needed if there is a well-functioning non-invasive blood pressure cuff and accurate pulse oximeter. However, if there is a high likelihood to need inotropes intra- or postoperatively, most practitioners will elect to place additional monitors preemptively.

Intraoperative: As with any anesthetic, the choice of medications and type of anesthesia will be guided by the underlying cardiac disease and the proposed surgery. Agents such as etomidate, opioids and ketamine have a favorable hemodynamic profile that allows for smoother intravenous inductions of patients with even the most complex congenital heart disease. Volatile agents can then be used at lower MAC values (0.5-1 MAC) for maintenance of anesthesia. While intubation with positive pressure ventilation is often undesirable in second and third stage single ventricle physiology, many surgeries require intraoperative paralysis for best conditions to be present. If so, limiting the peak inspiratory pressures and PEEP so that venous return is not impeded is key.

Because abdominal surgery is one of the most common non-cardiac procedures done in this patient population, the question of whether laparoscopic surgery is safe has been investigated extensively. With insufflation, changes in systemic vascular resistance as well as decreases in venous return have the potential to cause hemodynamic instability, especially in the patients with single ventricle physiology. Gillory et al. performed a 10-year retrospective review of 121 laparoscopic vs. 50 open procedures in children with congenital heart disease. They found no difference between groups with respect to instability.[13] Other studies have also demonstrated safety with laparoscopy in patients with a single ventricle, noting that insufflation pressures should be kept between 8-12 mm Hg and low flow.[14-15]

Postoperative: Finally, the decision to extubate the patient is multifactorial and depends on the length of the surgery, the amount of fluids administered, intraoperative hemodynamic stability, and postoperative pain management. Postoperative disposition needs to be considered as well. Depending on the complexity of the surgery and the patient's status, many patients should recover in an intensive care unit due to the potential for hemodynamic instability and the need for postoperative ventilation. When in doubt, the default should be to send the patient to the intensive care unit for closer observation following most emergency surgeries.

Anesthetic Management of Specific High Risk Pediatric Cardiac Patients

Single Ventricle: Patients with single ventricle physiology are some of the most high-risk patients to care for during non-cardiac surgery.[16] While there are many different anatomical variations that fall within the category of single-ventricle physiology, all of them have both systemic and pulmonary blood flow mix completely before leaving the heart. In the course of their management, these patients will undergo three staged cardiac surgical procedures, which result in varying sources of pulmonary and systemic blood flow. Consequently, following each stage, there will be different physiologic consequences and management principles.

Post-Stage I Palliation: In this shunt-dependent physiology, a systemic to pulmonary connection allows for pulmonary blood flow. In order to maintain patency of the shunt, these patients are often on some form of anti-coagulation. This is considered a somewhat fragile circulation, in which even small changes in oxygen, ventilation, pH, or temperature can tip the balance of pulmonary and systemic blood flow. The goal is to maintain SpO_2 in the range of 75-85%, avoiding high FiO_2, which can result in increased pulmonary blood flow at the expense of the systemic blood flow. Furthermore, since the single ventricle handles both the systemic and pulmonary venous return and outflow, it is very preload dependent, and increases in afterload are not well tolerated. Therefore, these patients should not be subjected to unduly long pre- operative fasting, and careful attention should be given to fluid management with regard to third space losses as well as blood loss. Maintaining SVR with inotropes and adequate intravenous fluids is imperative.

Post-Bidirectional Glenn and Fontan: The second stage of palliation, the Glenn operation, diverts the venous return from the superior vena cava (SVC) to the pulmonary arteries. The desaturated blood from the inferior

vena cava (IVC) continues to mix in the common atrium with the saturated pulmonary venous return, yielding an arterial oxygen saturation of approximately 85%. Partial diversion of the venous return to the pulmonary circulation significantly reduces the volume load on the ventricle, resulting in improved hemodynamics over the stage I palliation. In the third stage, the Fontan operation, the IVC blood flow is also diverted to the pulmonary bed, resulting in even higher pulmonary blood flow and higher saturations (85-92% while a fenestration is present).

Since passive flow from the SVC (Glenn) or the SVC and IVC (Fontan) is the source of pulmonary blood flow, it is more likely to be affected by increased intrathoracic or intra-abdominal pressure, volume status, PVR, and hemoglobin levels. While spontaneous ventilation is ideal with this physiology, the nature of many surgeries requires paralysis and positive pressure ventilation. Therefore, limiting peak inspiratory pressures and PEEP so that venous return is not impeded is key. Oxygenation is actually improved with mild hypoventilation ($PaCO_2$ of approximately 40-45 mm Hg). By improving cerebral vasodilation, there is better blood drainage from the cerebral vasculature into the SVC and ultimately the pulmonary bed for increased oxygen exchange.[17]

The goals of management, therefore, include the maintenance of adequate intravascular volume and appropriate PVR. Conditions that decrease venous return, such as hypotension, hypovolemia and tachycardia should be treated with appropriate fluid therapy. Factors that increase PVR, such as hypoxemia, hypercarbia, acidemia and excessive airway pressures, result in decreased pulmonary blood flow and hypoxia and therefore should be avoided.

Pulmonary Hypertension: Pulmonary hypertension is secondary to one of the following causes: left-sided heart disease in which high pressure is transmitted back to the pulmonary bed; increased left-to-right shunting resulting in significant pulmonary overflow; intrinsic pulmonary disease; or idiopathic. In all of these scenarios, intrapulmonary vascular changes develop with thrombosis, ultimately leading to fibrosis and obliteration of arterioles. This then places the patient at increased risk for a pulmonary hypertensive crisis. With sudden increases in PVR (due to hypoxia, hypercarbia, acidosis or sympathetic stimulation), the pulmonary artery pressure exceeds systemic blood pressure, and there is an acute drop in right ventricular function. In patients with an atrial level shunt, the patient will become cyanotic with right-to-left shunting. When no shunt is present, however, decreased pulmonary blood flow will result in decreased cardiac output and biventricular failure.[3]

Multiple studies have demonstrated that pediatric patients with pulmonary hypertension are at increased anesthetic risk.[18-19] The frequency of major complications is associated with the severity of baseline pulmonary hypertension. In patients with systemic or supra-systemic pulmonary pressures, the incidence of complications was significantly higher than those with sub-systemic pressures.[18] Predictors of perioperative mortality with pulmonary hypertension include a history of syncope, poor functional status, dysrhythmias, SpO_2 less than 85%, severe right ventricular dysfunction and Trisomy 21.

In patients with pulmonary hypertension, prevention of acute increases in PVR while under anesthesia is key. The time of induction can be especially difficult. Agents such as etomidate, opioids, or ketamine have all been shown to provide hemodynamic stability.[20] Active measures to avoid hypercarbia, hypoxia, and acidosis should be undertaken, including early controlled ventilation when appropriate. Adequate fluid resuscitation is also important. No specific anesthetic agent or technique will prevent pulmonary hypertensive crises in all patients. Rather, a balanced technique is used so that the detrimental effects of a higher dose of any one specific agent are avoided. In the event of a hypertensive crisis, a FiO_2 of 1.0, hyperventilation, correction of acidosis, and nitric oxide are the treatments of choice. Hemodynamic support and agents to improve right ventricular function are also needed.

Cardiomyopathy: Cardiomyopathy, an abnormality of the myocardium, is classified by etiology and physiology into the following categories: dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC) and unclassified.[21] Each of these subtypes has a specific clinical picture, with the vast majority eventually developing heart failure. In the POCA registry report from 2010, there was 50% mortality in patients with cardiomyopathy.[1] Patients with cardiomyopathy at highest risk of cardiac arrest under anesthesia are those with a shortening fraction of less than 16% on echocardiogram.

In many forms of cardiomyopathy, baseline blood pressure is relatively low secondary to diuretic therapy, use of ACE inhibitors, beta blockade and poor cardiac function. In the perioperative period, this is further exacerbated with dehydration when there is fasting. This dehydration and relative hypotension can complicate anesthetic induction and maintenance secondary to the vasodilatory effects of almost all anesthetic agents and the resulting decrease in preload. Kipps and colleagues, looking at anesthetic management in 26 patients with heart failure, found that approximately 38% had complications under anesthesia, the most common being significant

hypotension requiring inotropic agents.[22] As with pulmonary hypertension, the choice of anesthetic technique will most often be a balance of several agents at lower doses to avoid the negative effects of larger doses of any agent alone. Inotropic support is key in these patients to prevent worsening ischemia or the development of arrhythmias.

Obstructive Lesions: Obstructive lesions can occur anywhere along the ventricular outflow tract, including at the valve itself, above or below it. Certain disease states, such as Williams Syndrome, can be associated with both left and right ventricular outflow tract obstruction. Looking specifically at left ventricular outflow tract obstruction, which tends to cause more significant complications, there are several mechanisms whereby cardiac arrest occurs. With severe obstruction, the left ventricle becomes hypertrophied, increasing wall tension and oxygen consumption. The hypertrophy can also compromise coronary flow leading to subendocardial ischemia.[5]

In these patients, any agents that decrease coronary blood flow (decrease SVR or cause myocardial depression) or increase myocardial oxygen consumption (tachycardia or dysrhythmias) will potentially worsen ischemia and lead to cardiac arrest. Furthermore, anesthetic induction and emergence are associated with an increase in sympathetic activity, which can cause hypertension, tachycardia and increased oxygen consumption.

Anesthetic goals in these patients include the following: maintenance of preload, contractility, and SVR; continuation of normal sinus rhythm; preventing increases in PVR; and avoidance of anesthetic agents that cause tachycardia or significant vasodilation. Adequate hydration is key, with fluid boluses often given prior to induction. Etomidate and opioids are common induction agents. Ketamine, though it can cause some tachycardia, has been successfully used in pediatric patients with severe stenosis.[5] Dexmedetomidine, which will decrease heart rate and increase SVR, also beneficial properties and can be used as part of a balanced anesthetic technique. In case of worsening ischemia, seen as ST segment changes or dysrhythmias on ECG, prompt treatment with an alpha-agonist such as phenylephrine is critical. Improvement of the balance in myocardial oxygen supply and demand should be immediate as well. ECMO availability in the highest risk patients should be arranged prior to surgery to allow for the most rapid response possible if needed.

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Rational Use of Multimodal Analgesics

May L. Chin, M.D. **Washington, D.C.**

Introduction

Perioperative medicine continues to evolve toward better, more cost effective healthcare delivery, with emphasis on better patient experiences and outcomes. Although opioids have traditionally been the analgesic of choice for postoperative pain control, monotherapy using opioid analgesics alone is often inadequate and may be associated with significant side effects[1]in addition to morbidity from opioid related respiratory depression[2] and opioid abuse[3]. Optimal patient care now emphasizes collaborative efforts to improve perioperative experience and surgical outcomes, as in the Perioperative Surgical Home (PSH).[4] Effective perioperative pain control plays an important and essential role in achieving the desired outcomes in the PSH model. "Multimodal analgesia" coined more than two decades ago, refers to the use of a combination of pharmacologically different analgesics for additive or synergistic effects, in an effort to optimize the control of postoperative pain.[5]

This lecture will 1) review mechanisms of acute and persistent postsurgical pain, 2) discuss rational and evidence based use of multimodal analgesics and 3) examine the impact of multimodal analgesics on patient outcomes.

Nociception, Sensitization and Neuronal Plasticity

Tissue injury and inflammation result in the release of chemical mediators which activate high threshold nociceptors, A delta and C fibers. With peripheral sensitization the threshold for nociceptor firing is diminished resulting in amplication of signaling from the periphery. Non noxious stimuli now elicit pain (allodynia) and a painful stimulus produces an exaggerated pain response (hyperalgesia). The signals from the periphery enter the central nervous system in dorsal horn of the spinal cord where complex processing of the signals occur. The nociceptive signals from the periphery are modulated within the spinal cord and by descending excitatory and inhibitory mechanisms. The result of this complex interplay is ultimately transmitted to areas in the brain involved with sensory, motor, autonomic and emotional processing, resulting in the perception of pain. With surgical trauma and continuous nociceptive input from the periphery, the dorsal horn neurons become more excitable. The receptive field properties of these neurons expand such that low threshold A beta mechanoreceptors which normally do not produce painful sensations now do so. These changes ultimately result in a state of hypersensitivity called central sensitization, in which the nervous system demonstrates an enhanced response to noxious stimulation.[6]

Tolerance and hyperalgesia

Repeated C fiber stimulation leads to central sensitization and hyperalgesia. The development of hyperalgesia involves activation of excitatory amino acids which lead to intracellular events and nitric oxide production. Activation of the mu receptor by opioids ironically also enhances NMDA receptor activation through similar intracellular events, resulting in reduced potency of the opioid.[5] These events are thought to play a role in the development of tolerance to morphine suggesting that neural mechanisms leading to hyperalgesia and tolerance both involve NMDA receptor activation.[7, 8]

Targets for adjuvant analgesics

The main contributors to sensitization and pain include the NMDA receptors, sodium channels, calcium channels, descending modulation via serotonergic pathways, noradrenergic systems that activate alpha 2 adrenergic receptors, prostaglandins, cytokines and inflammatory mediators.

N-Methyl-D-aspartate (NMDA) receptor antagonists

NMDA receptors are activated by the excitatory neurotransmitter glutamate in the presence of tissue injury. Consequently, the NMDA receptor plays a major role in pain processing in the spinal cord whereby receptor activation results in a hyperexcitable state of the nervous system and increased pain. NMDA antagonists may

alleviate pain by the inhibition of central sensitization.[9] The NMDA receptor is a ligand gated ion channel permeable to calcium, potassium and sodium. At resting membrane potential, the NMDA receptor is blocked by a magnesium ion which is removed on depolarization allowing glutamate to activate the receptor.[10] The NMDA receptor is composed of several subunits. Some of these subunits are involved with CNS function; therefore an NMDA antagonist may produce undesirable psychotomimetic effects, memory impairment, ataxia and uncoordinated motor function.[9]

Ketamine is an anesthetic agent that has been in clinical use for the past five decades. Potential unpleasant CNS side effects such as hallucinations have discouraged widespread use of ketamine in anesthesia. However there is renewed interest in ketamine as an NMDA antagonist in the treatment of pain, especially with the understanding of the role of the NMDA receptor in neuronal hyperexcitability. Ketamine is a non-competitive antagonist that binds to the phencyclidine binding site of the NMDA receptor. It is available in as racemic ketamine which contains equimolar amounts of S (+) and R (-) and as the S (+) stereoisomer which is twice as potent. The S (+) ketamine has four times greater affinity for the NMDA receptor than the R (-) ketamine (5Mao). Ketamine has an elimination half-life of 80 to 180 minutes. The metabolite nor-ketamine is one third as potent and has a longer half–life and may contribute to the prolonged analgesic action of ketamine.[10]

Providing adequate analgesia for chronic pain patients who are opioid dependent has always been challenging. The perioperative use of ketamine has been reported to be helpful in these circumstances despite the lack of well conducted studies. There are several systematic qualitative and quantitative reviews of randomized trials on the use of ketamine in perioperative pain management.[8, 11, 12,13,14,15] The reviews collectively reported on large numbers of patients worldwide but several limitations were noted. In particular, there were large variations in clinical settings, the trials were relatively small, and different ketamine regimens and various routes of administration were utilized. Most of the studies reported reduced pain and analgesic consumption immediately and beyond the duration of action of ketamine when administered in the perioperative period. A small (sub anesthetic) dose of ketamine was noted to be safe and afforded opioid sparing but the reviews differed on whether opioid related side effects were decreased. The optimal timing for perioperative administration of ketamine is not clearly defined. Various dosing regimens have reported effective analgesia with ketamine given in various combinations of dosing such as precision, intraoperative, at wound closure and continuing for 48 to 72 hours postoperatively.[16, 17,18,19,20]

Recent efforts looking at the perioperative use of ketamine include prospective, randomized, double blinded trials in patients undergoing total hip arthroplasty in one[21] and major spine surgery in the other.[22] both demonstrated reduction in opioid use and decreased opioid consumption in opioid dependent patients with chronic pain. Pain was decreased at six months in those who received ketamine undergoing major spine surgery. The opioid dependent patients who underwent spine surgery received an initial dose of ketamine 0.5 mg/kg at induction followed by 10 mcg/kg/min infusion prior to incision and terminated upon closure. The patients for hip arthroplasty did not have a history of high opioid use. They also received ketamine 0.5 mg/kg at induction followed by an infusion for 24 hours at 2 mcg/kg/min.

An opioid administered by intravenous patient controlled analgesia (IV PCA) may be prescribed in the postoperative period in addition to ketamine. Although reports on the effectiveness were conflicting [8,14] a large prospective study of over one thousand patients found the combination of ketamine and morphine in IV PCA to be safe on the general nursing floor.[23] The same study also reported low pain scores and high patient satisfaction. In a randomized double blinded study, the administration of a small dose of ketamine at 250 mcg/kg (in addition to morphine), produced immediate and sustained analgesia in those patients resistant to morphine in the post-anesthesia care unit (PACU).[24] Patients who received ketamine reported better pain scores, a better feeling of wellbeing and wakefulness, higher oxygen saturation. They had minimal nausea and vomiting or ketamine related side effects.

Memantine is a long acting oral NMDA antagonist which is FDA approved for use in patients with Alzheimer's disease. Case reports describe use for chronic pain as in phantom limb pain and opioid tolerant cancer patients.[25, 26, 27]

Amantadine, another NMDA antagonist is available for both oral and parenteral delivery. It is primarily prescribed for Parkinson's disease, dementia and spasticity. Perioperative use has had mixed results; one study showed

parenteral amantadine to be ineffective in postoperative analgesia[27] another reported decreased postoperative opioid use.[29]

Dextromethorphan exhibits NMDA receptor antagonist property and a weak affinity for the mu opioid receptor. It is commonly prescribed as an antitussive agent is associated with few side effects. Clinical studies indicated that the administration of preoperative oral dextromethorphan resulted in an attenuated response to tourniquet pain[30] and that pre incisional dextromethorphan reduced postoperative morphine requirements.[31] However, a systematic review of the use of dextromethorphan in postoperative pain control did not report consistent analgesic or opioid sparing effects of the drug.[32] The authors were unable to recommend a dosing regimen for the drug nor could they recommend routine clinical use of dextromethorphan for postoperative pain control.

Voltage Gated Calcium Channel Blockers

In the postoperative patient, surgical trauma may lead to peripheral and central sensitization resulting in hyperalgesia and allodynia seen as movement evoked pain. Several recent reviews on the use of anticonvulsants in the postoperative period report opioid sparing effects, improvement in function and anxiolysis.[33,34,35,36,37,38]
Gabapentin and Pregabalin are structural analogs of the inhibitory neurotransmitter gamma-amino butyric acid (GABA), and both bind to alpha 2 delta subunits of voltage dependent calcium ion channels to produce antihyperalgesic effects.[39,40] A randomized placebo controlled double blinded study in healthy volunteers showed that gabapentin enhanced the analgesic effect of morphine.[41] Gabapentinoids are known to be effective in reducing acute postoperative pain and opioid consumption. One recommended dosing regimen would be gabapentin 1200 mg 2 hours before surgery and 600 mg tid from 1-14 postoperative days and for pregabalin 300 mg preoperatively and 150 mg bid postoperatively.[42] A systematic review of perioperative pregabalin reported decreased pain scores at rest and with movement and decreased opioid consumption. However pregabalin was associated with a higher incidence of sedation, dizziness and visual disturbance.[43] Further studies however are needed to identify the anticonvulsant with the best therapeutic profile, the optimal dose and duration of use, the prevention of persistent surgical pain, and the patient population that would benefit most from this adjuvant analgesic.

Serotonin and Norepinephrine

Descending inhibitory pathways in the central nervous system modulate the perception of pain through actions of serotonin and norepinephrine. Serotonin (5-hydroxytryptamine) is a monoamine neurotransmitter involved in pain processing. There are several different 5-HT receptor types such that serotonin can inhibit or facilitate nociceptive transmission. Serotonin and norepinephrine reuptake inhibitor drugs (SNRI) produce anti nociception and have been used in the treatment of certain chronic pain states. A systematic review of 15 studies reported insufficient evidence at this time for use of antidepressants for acute postoperative pain or for prevention of chronic postsurgical pain.[44]

Voltage Gated Sodium Channel Blockers

Local anesthetics disrupt nerve conduction by blocking voltage gated sodium channels. Several subtypes of sodium channels (Nav1.7, Nav1.8, Nav1.9) are highly expressed in nociceptors. The TRPV1 (transient receptor potential vanilloid 1) also found in nociceptors, and is activated by capsaicin followed by influx of sodium and calcium ions. Lidocaine analogues acting on TRPV1 channels block sodium channels and may be a future solution to a pain fiber specific block.[45] There is ongoing work to develop better local anesthetics to produce selective prolonged analgesia.[46]

Lidocaine is a local anesthetic that may be given intravenously. A systematic review of perioperative intravenous lidocaine reported benefits in abdominal surgery with reduced pain, opioid requirements and opioid side effects, as well as decreased length of hospital stay.[47] There were no beneficial effects were seen with perioperative intravenous lidocaine in other types of surgery such as hip arthroplasty, tonsillectomy or coronary bypass surgery.[48, 49]

Continuous use of local anesthetics at the surgical site have shown efficacy in improving analgesia and reducing opioid use and possibly reducing length of stay in a wide range of surgical procedures.[50,51] An alternate approach with a single injection of a long acting local anesthetic negating the use of catheters and pumps is appealing. Liposomal bupivacaine formulated for controlled release of bupivacaine is currently approved for surgical site infiltration only but clinical efficacy is variable.[52, 53]

Non-Steroidal Anti Inflammatory Drugs (NSAIDS)

Prostaglandins, produced in the periphery in the presence of inflammation and tissue injury, activate peripheral nociceptors. Spinal neurons may also produce prostaglandins in response to peripheral injury. COX inhibitors provide analgesia by inhibiting COX mediated production of inflammatory prostaglandins. Centrally, COX inhibition prevents NMDA and AMPA (alpha amino 3 hydroxy 5 methyl isoxazolpropionic acid) receptor activation and the development of central sensitization.[54]

NSAIDS are commonly prescribed in the perioperative period as part of a multimodal approach to optimize pain control. **Ketorolac,** the most commonly prescribed parenteral NSAID in the US has shown efficacy in the immediate postoperative period. A recent meta analysis[55] reported better pain control and less nausea and vomiting with a single dose of ketorolac as an adjunct analgesic. However there is no uniform consensus on the optimal dose of ketorolac.[55, 56, 57]

Non selective NSAID inhibition of prostaglandins can be associated with serious side effects which include gastric ulceration, renal dysfunction, and bleeding diathesis. Selective COX 2 inhibitors have been associated with fewer gastrointestinal side effects compared to the non-selective NSAIDS. Although there appears to be little difference in analgesic efficacy between the two groups[58] others have reported improved postoperative analgesia, decreased opioid use and opioid related side effects with perioperative use of celecoxib.[59]

Nonetheless concern for potential risks of surgical bleeding and impaired bone healing generate controversy regarding the use of both selective and non-selective NSAIDS in the perioperative period.[60] A meta-analysis of several randomized controlled trials showed a higher risk for postoperative bleeding after tonsillectomy with postoperative use of NSAIDS.[61] However, others have disagreed with this analysis, citing differences in the dosing of the drug, the duration of treatment, poor surgical technique, and that in some patients, the bleeding occurred at a time when the drug had been eliminated from the body.[62] Spine surgeons are often reluctant to prescribe NSAIDS in the perioperative period because of concern with impairment in bone healing. Animal and clinical studies suggest that NSAIDS can

potentially inhibit bone formation, healing, and fusion.[60] It is thought that COX 2 inhibitors may have an advantage since this effect has not been substantiated in humans even though evidence from animal studies suggest impaired bone healing with COX 2 inhibitors.[63]

Acetaminophen

Acetaminophen, also known as paracetamol, has analgesic and antipyretic properties. Even though the mechanism of action is largely unknown, it has a known safety profile and is used extensively in pediatric population. As an adjunct analgesic, intravenous acetaminophen 1g given over 24 hours postoperatively was effective for moderate to severe pain after orthopedic surgery.[64] A meta-analysis of paracetamol, non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors show a morphine sparing effect with each group. However, paracetamol may be less efficacious in decreasing morphine requirements but nsaids are associated with an increased risk of bleeding.[65]

Alpha 2 agonists

Alpha 2 agonists produce sedation and analgesia with minimal respiratory depression. There are 3 subtypes of alpha 2 adrenoreceptors that mediate the physiologic functions which produce sedation, analgesia, bradycardia and sympatholysis. The locus ceruleus is the predominant site for sedation and the spinal cord the main site for analgesia although peripheral and supra spinal sites are described.[66]

Dexmedetomidine, Clonidine

Clonidine is a less selective alpha 2 agonist compared to dexmedetomidine. It has been prescribed for analgesia and can be administered in several ways, namely: oral, parenteral, transdermal, neuraxial, by intra-articular injection or injection around peripheral nerves. Dexmedetomidine, a highly selective alpha 2, has a significantly shorter half-life and therefore easily titratable is administered for sedation and analgesia. Dexmedetomidine infusions using small doses (0.2 or 0.6 mcg/kg/hr) has been shown to produce easily reversible sedation and analgesia, associated with

stable cardio-respiratory function and therefore potentially useful in the intensive care unit and in the immediate postoperative period.[67]

A systematic review and meta-analysis looked at the effectiveness of perioperative use of alpha 2 agonists in almost 1000 out of 1800 patients.[68] Patients receiving clonidine or dexmedetomidine reported decreased postoperative morphine requirement and pain intensity and had less nausea. However long term effects, i.e. decrease in chronic postoperative pain is unknown.

Corticosteroids

Surgical trauma leads to inflammatory and stress responses and the production of cytokines which include the interleukins, tumor necrosis factor (TNF) and chemokines all of which contribute to pain. Corticosteroids inhibit phospholipase as well as cytokines, TNF and other inflammatory mediators and may be useful in reducing postoperative pain. A meta-analysis reviewed 2500 patients receiving three different dose range of dexamethasone with respect to opioid requirements and pain control.[69] Dexamethasone greater than 0.1 mg/kg IV decreased postoperative pain and opioid requirement. However the resultant hyperglycemia from steroid administration and risk of wound infection were not studied and the implications of these risks remain unclear.[70]

Outcomes

A Cochrane review on single dose analgesic studies show limitations in providing good pain relief [71]and a systematic review on the combination of two analgesics shows improved analgesic efficacy compared to either drug alone.[72] Using adjuvant analgesics in a multimodal approach has been shown to be beneficial in the perioperative period by reducing opioid requirement, side effects of nausea and vomiting, early recovery of bowel function and decrease in pain intensity.[58] Some studies have shown pain relief and facilitation of physical rehabilitation one month out from surgery[21] and some show improved pain three to six months beyond surgery.[22,73] The role of ketamine in multimodal analgesia continues to be better defined with higher quality studies. More information is needed from long-term outcome studies, on the minimum effective dose, and the side effect profile of the drug. At the present time, there is data to support that ketamine may be useful as an adjuvant analgesic in the opioid tolerant patient with a history of chronic pain although this deserves further studies particularly in the long term benefits and reduction of chronic postoperative pain.[74]

In a recent prospective study, the implementation of a quality management system (QMS) for the treatment of postoperative pain demonstrated clear benefits. Multimodal analgesia was individualized and the staff educated, resulting in better pain control, less analgesia related side effects and increased patient satisfaction.[75]

Even so, despite knowledge of pain mechanisms and reported benefits of non-opioid analgesics, pain control after surgery is often reported to be suboptimal.[75] There may be several reasons for this observation: (a) pain control not targeted to specific surgical procedures[76] (b) the lack of consistent use of multimodal analgesia techniques; [78, 79] and (c) inconsistent assessment of movement associated pain in postoperative patients.[80, 81]

Future directions toward improving postoperative pain control include (a) further investigation of the effect of acute pain and the use of opioid analgesics on the immune system. Acute pain and surgical stress may compromise immune function including suppression of natural killer (NK) cell activity. Retrospective analyses by some have reported reduction in cancer recurrence using regional analgesia [82,83]but others found conflicting results suggesting age and tumor type may play a role [84, 85] (b) further investigation into role of preventive analgesia; [86] (c) identifying patients who may be at risk for developing significant pain after surgery[87,79, 88] and (d) the use of pharmacogenomics in tailoring effective analgesic therapy.[79]

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Preoperative Evaluation in the 21st Century

Angela F. Edwards MD **Winston Salem, NC**

Organizing and Managing the Preoperative Process

Each year, over 200 million people undergo surgery worldwide and this population is becoming increasingly medically complex.[1] In the United States alone, 26% of all inpatient adverse events within the medicare population can be attributed to surgical procedures. Further, it is estimated that 44% of all perioperative adverse events are preventable.[2] With the number of ambulatory procedures rising and cost containment pressures escalating, anesthesiologists are encouraged to proceed with anesthetic management, minimize recovery times, and transition patients rapidly to home without risk of readmission. Consequently, chronically ill outpatients often recover in less time under direct observation prior to discharge home. [3, 4] Given these circumstances, it is essential for perioperative physicians to mitigate patient risk before the day of surgery. Pre-emptive medical optimization fosters opportunity for ideal outcome and minimizes risk of having incomplete information resulting in delayed or cancelled surgeries. Subsequently, this has a positive effect on operating room margin and improves financial solvency of institutions. [5] Indeed, having an effective preoperative process creates the ideal setting to optimize patients' medical conditions, ensure patient safety, appropriate selection, complete documentation and maximize efficiency within the preprocedural arena.

The primary goal of the preoperative process is to provide safe, reliable, risk reduction and medical optimization in a comprehensive manner. In order to do so, preoperative clinics have been developed to enhance operating room efficiency, decrease day of surgery cancelations, reduce hospital costs and improve the overall quality of patient care. Although preoperative programs differ in structure, staffing, financial support, and daily operations, they share the common goal of preoperative risk reduction in order for patients to proceed safely through the perioperative period. Effective preoperative evaluation occurs if processes are standardized to ensure clinical, regulatory, and accreditation guidelines are met while keeping medical optimization and patient satisfaction at the forefront. With careful triage based on comorbidities, functional status, and medications, certain low risk patients can often avoid unnecessary clinic visits while higher risk patients receive the necessary evaluations, consultations, and laboratory testing to ensure medical optimization. Well-resourced clinics in centralized locations have the ability to seamlessly provide preoperative services, ancillary testing (ecg, echo, lab testing and/or prehabilitation), and patient education in addition to maintaining effective communication across the surgical continuum. Collaboration and teamwork in a multidisciplinary context is paramount to such a program's success.

Several models of preoperative care have been previously described in the literature. [6] While, no current universally accepted, standard model exists, key components and leadership are necessary to establish and maintain a successful preoperative process. The first of which is to determine which patients are recommended to have in-person visits to a preoperative clinic. Triage systems have been developed to assist referring surgeons and proceduralists choose appropriate patients for in-person clinic visits. Such tools may be either paper or electronic, depending on the resources of the health care system. Historically, triage has been proposed using medical comorbidities, medication lists, and American Society of Anesthesiology classification to assess physical status and optimization.[7] With this, ASA class 1 and 2 patients could be triaged to remote telephone screens, whereas ASA class 3 and 4 patients could require in-person consultation. Phone screening nurses may collect critical information on the ASA 1 and 2 type patients to confirm demographic information, medical optimization as well as provide pre-procedural education. Higher risk patients with complex medical and social issues can be identified and triaged to in person visits with a trained physician or advanced practice provider. During this time, risk stratification and medical optimization of comorbidities can be ensured such that postoperative risks are minimized. Preoperative identification and management of high-risk patients with complex medical and social issues prior to their surgical admission has been shown to increase patient safety and satisfaction[8,9] as well as improve efficient utilization of operating room resources.[12] Preoperative clinic visits have been shown to reduce unnecessary testing, subspecialty consultations, and decrease hospital stay.[9, 11] Further, preoperative interventions that reduce risk of postoperative complications have led to significant cost savings.[34] It has been well documented that centralizing and

standardizing even part of the preoperative process through obtaining outside records, completing history and physical examinations, finalizing surgical, anesthesia, and nursing assessments increases operating room efficiency and decreases costs. The direct and indirect savings achieved by minimizing redundancy, avoiding day of surgery delays and cancellations, and ensuring appropriate documentation and coding offset direct expense of establishing and maintaining a preoperative assessment clinic.[6, 13]

Benefits of developing an effective preoperative clinic:

- Decreased surgical delays and cancelations due to non-medical issues
- Decreased perioperative morbidity and mortality
- Reduction in excessive and unnecessary testing and subspecialty consults
- Increased patient and surgeon satisfaction
- Increased regulatory compliance and operating room efficiency
- Improving information transfers; clean charts (consents, history and physical exams, etc.)
- Ensuring patient readiness promotes efficient operating room turnover times
- Improved patient satisfaction and education; opportunity for shared decision making
- Improved compliance with preoperative instructions (surgical & anesthesia)
- Implementing care coordination in a multidisciplinary context

Furthermore, well-established preoperative clinics are often able to coordinate perioperative services such that components of peri-procedural care can be addressed before the day of surgery. Preoperative medical optimization through streamlined evidence-based clinical algorithms, informed consent with shared decision making, and postoperative discharge planning can all be addressed early in the preoperative process. Ideally, the preoperative clinic sets the standard for perioperative care and is the model of delivery for all peri-procedural processes in a given healthcare system.

Developing a Preoperative Clinic

As with most clinics, the operational plan is the specific action plan developed to meet goals and objectives of the program, typically set forth by the institution. Prior to initiating a development plan, specific problem areas should be highlighted as target areas to address. As a general rule, the goals noted in the following tables can be used as a springboard for determining which services will be delivered by the preoperative program, keeping current and future scope in mind. Most important, the design and development of the preoperative clinic must serve the goals and objectives well and target specified areas of improvement.

Preoperative Process Goals

Improve Patient Care (Clinical Goals)

1. Provide a comprehensive preoperative evaluation; identify and optimize medical comorbidities to minimize risk.
2. Develop and implement individualized perioperative care plans; early planning for discharge home.
3. Communicate effectively with perioperative team to facilitate care planning
4. Consistently apply evidence-based, standardized, condition-specific protocols for preop testing
5. Perform detailed review of medications and provide perioperative medication instructions
    a. Include any new preoperative medications and maintenance of the patient's chronic medications
6. Provide patient education and counseling to ensure informed consent
7. Reduce anxiety, increase patient participation and promote enhanced recovery opportunities

Initiate Transitional Care Planning

1. Plan for the appropriate level of postoperative care
2. Provide case management services planning for post-discharge needs; minimizing risk of readmission

Improve Perioperative Care (Non-Clinical Goals)

1. Continual process improvement revising protocols as evidence develops improving patient outcomes
2. Distribute protocols institution-wide as the standard of care for all peri-procedural patients
3. Provide leadership in the perioperative services across service lines and department
   - Provide central location to obtain perioperative information and coordinate care
   - Complete clinical documentation and ensure informed consent
   - Confirm chart completion
   - Maintain compliance with all with regulatory standards
4. Provide patient and family education regarding perioperative processes, establishing expectations
5. Improve perioperative efficiency

An effectively structured preoperative clinic is the ideal venue to optimize patient health prior to surgery and coordinate perioperative services for optimal outcomes. Clinic structure, staffing, and overall organization depend on institutional goals and targeted initiatives. As perioperative physicians, anesthesiologists are ideally positioned to lead preoperative processes and guide clinic workflow to ensure patient and institutional goals are met. [14] Nevertheless, multidisciplinary collaboration and communication are continually required to ensure programmatic success.

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ANESTHESIOLOGY 2017
BOSTON OCTOBER 21-25

Preoperative Evaluation in the 21st Century

David L. Hepner, M.D., M.P.H. **Boston, MA**

Each year, over 200 million people undergo surgery worldwide and this population is becoming increasingly medically complex.[1] In the United States, 26% of all inpatient adverse events within the Medicare population are attributable to surgery and procedures.[2] Further, the number of ambulatory procedures performed now exceeds those done on an inpatient basis.[3-4] In such a progressively challenging environment, with an estimate that 44% of adverse perioperative events are preventable, it is essential that the risk of perioperative complications be mitigated. Also, the financial solvency of operating rooms in a fragmented health care system may be jeopardized by incomplete patient information that leads to delayed and cancelled surgeries.[5] As a result, having a sound preoperative process or preoperative clinic creates the ideal setting to optimize the patient's medical condition, ensure patient safety, selection, and maximize economic efficiency within the pre-procedural arena.

Appropriate Pre-Procedural Testing

Preoperative Assessment Testing Clinics coordinate preoperative surgical, anesthesia, nursing and laboratory care. Such clinics have been noted to lead to efficiencies in perioperative care by seeing most patients days before the surgery. The prior history, medical records, previous tests and consultations are reviewed, and a medical history and physical examination are conducted. Laboratory testing, electrocardiogram, and chest x-ray should be ordered if necessary, and it is essential to determine which patients need further workup or consultations in order to assess the patient's readiness for surgery.

The perceived benefit of risk stratification based on results of preoperative testing may be considered to vary with surgical risk. What is the potential that screening tests will assist in risk stratification and management? A number of institutions vary preprocedure testing guidelines based on the risk of the procedure, on the assumption that routine screening is unlikely to impact risk stratification for low risk procedures. Preoperative testing should be based on patient's comorbidities (physical status), on the type of surgery (operative risk) and on findings from the history and physical examination. It is important to avoid repetition of prior testing if there is no change in the patient's condition, and to avoid testing in healthy patients having minimally invasive procedures. Routine testing does not increase safety or the possibility of surgery cancellation, even in elderly patients with multiple comorbidities, for minimally invasive procedures. In a study randomizing approximately 20,000 patients, Schein et al demonstrated that routine screening testing had no impact on risk management and outcome in cataract surgery.[6]

There is no value for ordering laboratory tests solely because of planned surgery. Common tests ordered include urinalysis, hematocrit, white blood cell count, platelet count, general chemistry labs (serum sodium, potassium, chloride, bicarbonate, glucose, and blood urea nitrogen), prothrombin time, partial thromboplastin time, chest x-ray, and electrocardiogram. It has been demonstrated that in close to 50 percent of cases, these tests have been ordered for patients without recognizable clinical indications. Despite twelve percent of these routine tests being abnormal in one study, only 0.5% led to a change in management.[7]

It has been estimated that the annual cost of preoperative medical testing for all types of surgery in the United States was as much as $30 billion in the 1980s with unnecessary diagnostic testing being a substantial component.[8] The value of routine preoperative medical testing has also been questioned.[6] In a study of nearly 20,000 patients undergoing elective minor surgery, patients were randomized to no testing or a standard battery of tests, including ECG, CBC, electrolytes, urea nitrogen, creatinine, and glucose. There were no differences between the two groups in the overall rate of intraoperative complications. Therefore, routine preoperative medical testing does not increase the safety of minor procedures.

Chest X-rays are ordered frequently as part of a routine admission or preoperative evaluation even though available data does not support this practice. Chest X-ray is one of the most expensive tests ordered, it is not predictive of inpatient or postoperative pulmonary complications and very rarely leads to a change in management or cancellation of elective surgery.[9,10] For these reasons, the American College of Radiology recommends against routine admission and preoperative Chest Radiography.[11]

Many physicians express the fear of increased medicolegal risk if they do not routinely order screening or preoperative tests. It could be argued from a medicolegal standpoint that it is better not to order an unnecessary test if the next step to take in the event of an abnormal result is unclear. Should a clinically insignificant abnormal laboratory test finding be uncovered but nothing done, legal action may result at a later time. A complication unrelated to the abnormal result may develop at some point in the future and be blamed on the lack of follow-up.

In a recent population-based study evaluating preoperative blood work prior to low risk surgeries including ophthalmologic surgery, Kirkham and colleagues report that routine blood work was done prior to nearly a third of low-risk, mainly ambulatory, surgeries.[12] They demonstrate that comorbidities, age, and preoperative medical consultation were associated with routine blood testing. More importantly, they also found that there was significant variation between institutions. Geographic location of surgery was the strongest predictor for preoperative laboratory testing.[12] Similarly, Chen et al. recently demonstrated that preoperative testing before cataract surgery was more likely to be associated with the practice patterns of the ophthalmologist and whether patients had a preoperative visit rather than with patient comorbidities.[13] Over fifty percent of patients underwent a preoperative test prior to cataract surgery,[13] despite significant evidence and national guidelines against the utility of routine preoperative testing.[14,15] The authors suggest that providing institutions and individual providers feedback about rates of testing has the potential to reduce low value care.[12]

Recently, multiple primary care and specialty physician groups joined forces to create the '*Choosing Wisely'* campaign, aimed directly at decreasing the burden of unnecessary testing.[16] Each of the participating professional physician societies provided a list of five tests that should be performed less often, and the necessity of which should be questioned by physicians and patients when suggested. The American Society of Anesthesiologists is a partner in the Choosing Wisely Campaign, and is encouraging ongoing dialogue between patients and anesthesiologists to eliminate unnecessary tests and procedures.[17] Common low-value tests to question in anesthesiology include baseline laboratory studies in healthy patients without significant systemic disease when blood loss is expected to be minimal.[18] Even though baseline laboratory studies are discouraged in low risk patients based on low impact on quality, high cost of care, and weak evidence for their recommendation, they were still ordered in a third to half of patients in recent studies.[12-13]

The problem is not only the unnecessary test, but the actions taken as a result of an abnormal test. A false positive result, or an abnormal result that may not affect the anesthetic or surgical management, can lead to further testing, consults, and procedures that incur additional costs and potential complications. In an era of value-based medicine, the only justification of preoperative screening is that the health benefits outweigh the health risks and are worth the dollar costs. Laboratory tests are not good screening devices.[19]

Preoperative Evaluation

The most recent revision of the ACC/AHA perioperative guidelines provides an algorithm for evaluation and testing.[20] Current guidelines for cardiac risk stratification rely on urgency of procedure, stability of disease, clinical risk predictors including relative risk of surgery and functional capacity. Perioperative testing should only be conducted if it will impact decision making towards the surgery or perioperative care.[20] However, routine clinical evaluation is neither completely sensitive nor specific for cardiac risk estimation due to the inability to assess the functional capacity in some patients with orthopedic, vascular or thoracic disease.

Cardiac risk factors are generally utilized as clinical predictors for coronary artery disease and are elicited based on the history and physical examination. The most recent perioperative guidelines continue to use the revised cardiac risk index (RCRI) developed by Lee and colleagues for the prediction of heart disease for stable patients.[21] The RCRI identified six independent risk correlates, including ischemic heart disease, congestive heart failure, cerebral vascular disease, high risk surgery, diabetes mellitus (insulin dependent) and chronic renal failure (creatinine>2.0 mg/dL), where increasing number of risk factors correlated with increased risk for major cardiac complications. Not only is it essential to take into account the patient's cardiac risk factors, but also the relative risk of surgery in order to appropriately develop guidelines for preoperative testing. For this reason, the algorithm combines medical conditions and surgical risk for perioperative major adverse cardiac events. The relative risk of surgery is based on the risk of developing cardiac death and myocardial infarction during noncardiac surgery and is now divided into low and high risk procedures (previously low, intermediate and high). The risk of cardiac events ranges from <1% for low risk procedures to ≥1% for high-risk procedures. The most recent perioperative guidelines only considers intraperitoneal, intrathoracic, or suprainguinal vascular as high risk procedures.[20] The presence of two or more of the above named risk correlates place the patient at high risk for perioperative adverse cardiac events. For high risk procedures, one or more risk factors place the patient at high risk for major adverse cardiac events.

The probability of silent cardiovascular disease could be elicited by the presence of obvious symptoms during the history taking. The patient's functional capacity is assessed by daily living activities and exercise capacity, and is used to evaluate symptoms of potential cardiovascular disease such as shortness of breath and chest pain.[22] Functional capacity is also a predictor for perioperative cardiac events. It is necessary to determine the

patient's functional capacity for those patients at elevated risk for major adverse cardiac events. Patients that can do at least 4 METS can reasonably proceed to the operating room without further cardiac testing. Patients at elevated risk with poor functional capacity may benefit from further cardiac testing (pharmacologic stress testing). However, this should only be done if the results will change decision making or the perioperative care plan. If testing will not impact decision making or management care, then it is reasonable to proceed to surgery according to guideline directed medical therapy. Alternatively, consider alternative management strategies such as noninvasive treatment or palliation.

ADDITIONAL CARDIAC TESTING

Perioperative assessment for prevention of cardiac complications is an important task of the anesthesiologist. Cardiac preoperative evaluation of the noncardiac patient relies on information from multiple sources: the medical record, history, and physical examination; and findings from medical tests, including electrocardiogram (ECG). As outlined above, other factors to be considered include coexisting medical disease, clinical risk factors, and the patient's functional capacity.

Since risk assessment relies on a medical history and physical examination, it is important to be more selective in the ordering of cardiac tests. A test is likely to be indicated if it can identify abnormalities and change the diagnosis and management plan, or the patient's outcome.[23] Excessive cardiac testing is expensive, and it may delay the operation and place the patient at risk for unnecessary interventions. It has been shown that an efficient anesthesiologist-directed preoperative clinic can decrease non-invasive diagnostic testing.[24]

Electrocardiogram

Routine ECGs have been reported to be abnormal in 7.0-42.7% of cases in 12 different studies but led to changes in management in only 10% of these cases.[25] The rate of ECG abnormalities and changes in management increased when the ECG was ordered based on the history and physical examination. Important clinical characteristics to consider when making a decision to order an ECG include cardiovascular or respiratory disease, multiple cardiac risk factors, and the surgical risk. There is currently no consensus regarding a minimum age for obtaining an ECG prior to a noncardiac surgery.[25] Patients at higher risk of having a significantly abnormal ECG are those older than 65 years of age or who had a history of heart failure, high cholesterol, angina, myocardial infarction, or severe valvular disease.[26] The ACC/AHA 2014 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery discourage preoperative ECGs in asymptomatic persons undergoing low-risk surgical procedures regardless of age.[20] Even though ECG abnormalities are more common in older patients, they are not predictive of postoperative complications.[27] Therefore, a preoperative ECG ordered routinely in those older than 50-60 years does not seem to add any value in predicting postoperative complications beyond cardiac risk factors. The ACC/AHA 2014 perioperative guidelines state that preoperative resting 12-lead electrocardiogram (ECG) is reasonable for patients with known coronary heart disease, significant arrhythmia, peripheral arterial disease, cerebrovascular disease, or other significant structural heart disease. Furthermore, they state that a preoperative resting 12-lead ECG may be considered for asymptomatic patients, except for low-risk surgery.

Echocardiogram

A preoperative echocardiogram is recommended in patients with clinically suspected moderate or greater degree of stenosis or regurgitation if there is any progression of clinical status or worsening of the physical examination. Even if there have been no changes in clinical status, an echocardiogram is recommended if it has been at least a year since the last one.

The current guidelines consider assessment of left ventricular function reasonable for patients that have dyspnea of unknown origin or worsening dyspnea with a history of heart failure. It is also reasonable to repeat echocardiography in patients with heart failure that have not been reevaluated during the last year.

Pharmacologic stress test

Patients at high cardiac risk with poor or unknown functional capacity may benefit from further cardiac testing to assess for myocardial ischemia if the results may lead to a change in management. It is also reasonable to perform a stress test in patients at high cardiac risk with unknown functional capacity to assess for functional capacity if it will lead to a change in management. Routine screening with noninvasive stress testing is not useful for patients at low risk for noncardiac surgery.

ANESTHESIOLOGY 2017
BOSTON OCTOBER 21-25

SUMMARY

The preoperative assessment provides an invaluable opportunity to stratify, manage and optimize risk. Risk stratification, management, optimization, documentation, and communication to the care team will allow all providers involved in preoperative care the opportunity to ensure the best possible patient outcomes. Additional tests, evaluations and consultations should only be done if the information to be obtained will result in changes in the perioperative management of the patient.

Moving away from preoperative testing to the practice of preoperative medicine

BobbieJean Sweitzer, MD, FACP **Chicago, Illinois**

Major surgery is associated with significant physiologic stress and adverse outcomes short- and long-term.[28] Approximately 15% of patients having in-patient non-cardiac surgery are at risk for serious complications including disability or death. Worldwide, 200-250 million patients have surgery yearly; many are aged with severe comorbidities and advanced disease. Up to 2.5 million patients will die (1% risk) and 12.5 million will have costly adverse events (5% risk).[29] A little over 12% of patients account for 80% of postoperative deaths.[30] Mortality rates vary widely across hospitals and countries. Evidence suggests that high-risk patients are often not identified preoperatively, and proven strategies to lower risk are not implemented. Risk assessment can lead to changes in medical management, planned anesthesia and surgery, postoperative care, or recommendations to avoid surgery. Advanced age is a strong predictor of postoperative mortality and morbidity from cardiovascular (CV), pulmonary, and infectious causes.[31] Elderly patients >75 years have twice the risk of serious morbidity and 3-7 times the risk of dying compared to younger patients. The frail elderly and those undergoing cancer procedures are at particular risk. Frailty independently predicts postoperative complications, length of stay (LOS), and discharge to an assisted-living facility.[31] Determination of a frailty score supplements other risk models. Impaired cognition, low albumin, previous falls, low hematocrit, functional dependence, and multiple co-morbidities are associated with 6-month mortality and inability for discharge home postoperatively.

Most patients with chronic dyspnea of unclear etiology have one of four diagnoses: asthma, COPD, interstitial lung disease, or cardiac dysfunction . Miscellaneous conditions, including deconditioning, account for the rest. The history and physical examination leads to diagnoses in two thirds of cases. Initial testing includes an ECG, hematocrit, arterial blood gases, thyroid function tests, chest radiograph, spirometry, and oximetry (resting and after walking several feet).

Postoperative pulmonary complications (PPO) incur the highest costs. PPO reduce median long-term (5-10 years) survival by 90%. Established risk factors for PPO include a history of cigarette use (current or exceeding 40 pack-yrs); ASA-PS $\geq$ 2; age $\geq$ 70 years; COPD; neck, thoracic, upper abdominal, aortic, or neurologic surgery; procedures $\geq$ 2 hr, general anesthesia (especially with intubation); albumin concentration < 30 g/L; inability to walk 2 blocks or climb 1 flight of stairs; or a BMI $\geq$ 30.[32] Heart failure (HF) is one of the strongest predictors of PPO. Asthma, arterial blood gas, chest radiograph or pulmonary function test (PFT) results are not predictive of PPO. Risk is greater with recent exacerbations, prior PPO, recent hospitalizations, or intubations for asthma. Some risk factors for PPO are modifiable. Exacerbations or infections must be improved whenever possible. Antibiotics, bronchodilators and steroids, or delay of surgery are important in high-risk patients. Delaying surgery up to one month before lung resection in high-risk, cancer patients with respiratory compromise for "prehabilitation" is associated with short- and long- term survival. Changes in management, including altering the surgical procedure, alternatives to general anesthesia, and epidural pain management are effective in decreasing PPO.

Exposure to tobacco, directly or second-hand, increases perioperative complications.[28] Smoking is associated with 40% increased odds of 30-day mortality and 30%-100% increased odds of morbidity, including surgical site infection, unplanned intubation, pneumonia and sepsis. Smoking decreases macrophage function, negatively impacts coronary flow reserve, and causes vascular endothelial dysfunction, hypertension and ischemia. Smokers require longer hospital stays and need postoperative intensive care more than non-smokers. A recent systematic review found no increased adverse events with quitting smoking soon before surgery (i.e., within 8 weeks).[33] Benefits are evident with cessation 3-4 weeks before surgery. Patients should be encouraged to quit smoking at any point preoperatively. Soon after quitting, toxic substances and carbon monoxide and cyanide levels decrease, improving wound-healing and oxygen delivery and utilization. Lower nicotine levels improve vasodilatation.

Renal disease increases perioperative risk, especially cardiovascular complications. Chronic kidney disease (CKD) is included in several risk scores. A creatinine $\geq$ 170 µmol/L is an RCRI risk factor equivalent to known stable ischemic heart disease in predicting cardiac risk.[20-21] Estimated glomerular filtration rate (eGFR) is a more

accurate measure of renal function, especially for less severe disease. The eGFR predicts short- (< 30 day) and long-term mortality.[34] Even mild disease (eGFR <60 mL/min/1.73 m^2) is associated with a threefold risk of death within 30 days and mortality and CV events long-term. Preoperative kidney disease is the strongest predictor of postoperative renal failure. Risk factors for CKD include age ≥55 yrs, smoking, diabetes, hypertension, dyslipidemia and HF.

Severe liver disease increases perioperative risk, especially with major surgery. Predictors of increased risk include Child-Pugh-Turcotte class C, MELD (Model for End-stage Liver Disease) score >15, acute liver failure, acute alcoholic hepatitis and a serum bilirubin >188 μmol/L. Renal insufficiency in association with hepatic disease causes a particularly poor prognosis. The highest risk surgeries are abdominal (including cholecystectomy), cardiac and emergency procedures, and those with high blood loss. Complications in surgical patients with cirrhosis include pneumonia, infections, and renal and respiratory failure. MELD scores can be calculated with creatinine and bilirubin levels and the INR.[35]

Malnourished patients have significantly higher rates of morbidity or mortality especially poor wound healing, increased LOS and infections. Low albumin levels predict mortality and morbidity. Adequate perioperative nutritional support decreases postoperative complications. Even mild preoperative anemia is associated with increased 30-day mortality.[36] Hemoglobin <8 g/dL is associated with a 16-fold increase in mortality. Morbidity is increased with mild-moderate anemia. In patients with CV disease, diabetes, or CKD and anemia, the perioperative mortality is twice that with the underlying disease alone. Perioperative transfusions are associated with increased morbidity and mortality. A restrictive transfusion strategy (maintaining hemoglobin 7-9 g/dL) is as effective, if not superior, to a liberal approach (hemoglobin of 10-12 g/dL) in critically ill patients, with the possible exception of those with unstable coronary syndromes. Efforts to diagnose and correct anemia preoperatively, especially for elective surgeries, in the elderly, in patients with other diseases or for surgeries with significant blood loss is necessary.

SUMMARY

Optimal preoperative patient preparation is essential if risks are to be lowered. Further research and development of evidence-based protocols are needed. Optimal results require a multidisciplinary approach with care providers with various clinical skills. A starting point is to use a combination of age, type of procedure, co-morbid conditions and biomarkers to stratify patients. Low-risk patients can proceed to surgery without special preparation. High-risk patients must be evaluated by a specialist in preoperative medicine and undergo advanced testing and prehabilitation if needed before proceeding to surgery in specialized centers.

Organizing and Managing the Preoperative Process

Angela F. Edwards, M.D **Winston Salem, NC**

The primary goal of a preoperative process is to provide safe, reliable, risk reduction and medical optimization in a comprehensive manner. In order to do so, preoperative clinics have been developed to enhance operating room efficiency, decrease day of surgery cancelations, reduce hospital costs and improve the overall quality of patient care. Although preoperative programs differ in structure, staffing, financial support, and daily operations, they share the common goal of preoperative risk reduction in order for patients to proceed safely through the perioperative period. Effective preoperative evaluation occurs if processes are standardized to ensure clinical, regulatory, and accreditation guidelines are met while keeping medical optimization and patient satisfaction at the forefront. With careful triage based on comorbidities, functional status, and medications, certain low risk patients can often avoid unnecessary clinic visits while higher risk patients receive the necessary evaluations, consultations, and laboratory testing to ensure medical optimization. Well-resourced clinics in centralized locations have the ability to seamlessly provide preoperative services, ancillary testing (e.g. ECG, echocardiogram, laboratory testing and/or prehabilitation), and patient education in addition to maintaining effective communication across the surgical continuum. Collaboration and teamwork in a multidisciplinary context is paramount to such a program's success.

Several models of preoperative care have been previously described in the literature.[37] While, no current universally accepted standard model exists, key components and leadership are necessary to establishing and maintaining a successful preoperative process. The first of which is to determine which patients are recommended to have in-person visits to a preoperative clinic. Triage systems have been developed to assist referring surgeons and proceduralists to choose appropriate patients for in-person clinic visits. Such tools may be either paper or electronic, depending on the resources of the health care system. Historically, triage has been proposed using

medical comorbidities and/or American Society of Anesthesiology classification to assess physical status and optimization.[38] With this, ASA class 1 and 2 patients could be triaged to phone screens, whereas ASA class 3 and 4 patients require in person consultation. Phone screening nurses may collect critical information on the ASA 1 and 2 type patients to confirm demographic information, medical optimization, as well as providing pre-procedural education. Higher risk patients with complex medical and social issues can be identified and triaged to in person visits with a trained physician or advanced practice provider. During this time, risk stratification and medical optimization of comorbidities can be ensured such that postoperative risks are minimized. Preoperative identification and management of high-risk patients with complex medical and social issues prior to their surgical admission has been shown to increase patient safety and satisfaction,[39-40] as well as improve efficient utilization of operating room resources.[41] Preoperative clinic visits have been shown to reduce unnecessary testing, subspecialty consultations, and decrease hospital stay.[42-43] Further, preoperative interventions that reduce risk of postoperative complications have led to significant cost savings. It has been well documented that centralizing and standardizing even part of the preoperative process through obtaining outside records, completing history and physical examinations, finalizing surgical, anesthesia, and nursing assessments increases operating room efficiency and decreases costs. The direct and indirect savings achieved by minimizing redundancy, avoiding day of surgery delays and cancellations, and ensuring appropriate documentation and coding offset direct expense of establishing and maintaining a preoperative assessment clinic.[44]

Benefits to developing an effective preoperative clinic include the following:

- Decreased surgical delays and cancelations due to non-medical issues
- Decreased perioperative morbidity and mortality
- Reduction in excessive and unnecessary testing and subspecialty consults
- Increased patient and surgeon satisfaction
- Increased regulatory compliance and operating room efficiency
- Improving information transfers; clean charts (consents, history and physical exams, etc.)
- Ensuring patient readiness promotes efficient operating room turnover times
- Improved patient satisfaction and education; opportunity for shared decision making
- Improved compliance with preoperative instructions (surgical & anesthesia)
- Implementing care coordination in a multidisciplinary context

Well-established preoperative clinics can coordinate services such that most, if not all, components of perioperative care are brought to the patient and discharge planning can be initiated before the patient leaves the clinic. Medical optimization, chart completion, shared decision making and postoperative care coordination can all be addressed early in the preoperative process. Ideally, the preoperative clinic sets the standards for care and is the model of delivery for all preoperative processes in a given healthcare system.

The operational plan is the specific action plan developed to meet goals and objectives of the preoperative program. The goals noted in the following tables can be used as a springboard for determining which services will be delivered by the preoperative program, keeping current and future scope in mind. Furthermore, the design and development of the preoperative clinic must serve the goals and objectives of the program well.

Goals of the Preoperative Process

Direct Patient Care

Provide comprehensive preoperative evaluation

• Identify, communicate, and minimize the patient-specific risks of surgery and anesthesia
• Consistently apply evidence-based, standardized, consistent, condition-specific protocols for preoperative testing
• Use goal-directed patient medical optimization to reduce case delays and cancellations
  – Develop and implement individualized perioperative care plans
• Perform detailed review of patient medications and give patient-friendly preoperative medication instructions
  – Include any new preoperative medications and maintenance of the patient's chronic medications

Initiate transitional care planning

• Plan the appropriate postoperative level of care
• Provide case management services to plan for post-discharge needs

Provide patient education and counseling

• To reduce anxiety, increase participation and enhance recovery after surgery

Obtain or confirm consent - Confirm the presence of anesthesia & surgical consent prior to surgery

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Indirect Patient Care and Non-Clinical Goals

Model Process Improvement

- Create standardized protocols to improve patient outcomes and decrease unnecessary testing
- Distribute protocols as the standard of care for all periprocedural patients

Centralize medical information and coordinate perioperative care

- Provide leadership in the perioperative services across service lines and department
- Manage tasks associated with perioperative patient care
  - Coordinate chart readiness, control information systems, other pertinent tasks
  - Comply with regulatory standards

Improve Perioperative Efficiency and Finance

Perform Research and Provide Education

Surgical Appropriateness

Angela M Bader MD, MPH **Boston, MA**

Most efforts to improve the quality of surgical care in the United States have been programs to either credential and certify providers, or measure and reduce surgical complications. The greatest unmet challenge in surgical quality is how to address *appropriateness*, i.e., to ensure that every decision to perform an operation fully reflects the conditions, circumstances, and values of individual patients. Appropriateness in surgery requires: 1) the best clinical evidence (right operation), 2) a qualified surgeon (right provider); 3) a healthcare facility that has the necessary resources to perform the operation safely (right place), and 4) a patient who is well-informed and meaningfully involved, and who is undergoing surgery that meets his or her individual preferences and values (right patient). Institutions and programs exist to address the appropriateness of provider and place, including board certifications, hospital privileging procedures, certification, and "center of excellence" designations. In contrast, the need to ensure that decisions for surgery reflect individual patients' values and preferences (right patient) is not as easily addressed with a programmatic or institutional approach, and has thus received inconsistent attention. While surgery often offers symptom relief or improved health status (e.g. reducing chance of heart attack or stroke), surgery is not without risk. Individual patients vary in how much they are bothered by their symptoms, how much they desire to reduce the chance of future health problems, and how much risk of surgical complications they are willing to accept. Given this variability, clinicians, healthcare consumers, and researchers have recognized that surgical decision making must be "patient-centered" and shared between patients and providers to ensure that decisions are of high quality, and procedures are selected appropriately. Health care organizations caring for patients undergoing surgical procedures must develop effective systems to ensure that all information, both clinical and nonclinical, is available throughout the episode to ensure high quality decision-making that integrates patient preferences, values and goals.

To achieve patient-centered care, providers need to ensure that patients are well informed and that medically appropriate treatments address patients' needs, wants and preferences. Decision quality is an important indicator of patient-centered care and an outcome relevant for surgical decision making. Prior research suggests that the patient's viewpoint is often absent when treatment decisions are made. In a study assessing the quality of decision making by surveying orthopedic surgeons (and not patients), reported deficits were related to fostering the patient's involvement in making the decision, and making attempts to ensure the patient's understanding.[45] Patients with chronic multiple comorbidities are particularly at risk; in a study of outpatient discussions of primary care doctors and surgeons regarding clinical decisions, only 9% overall met the criteria for complete informed decision making; less than 0.5% of intermediate or complex patients met this criterion.[46] Physicians rarely explored patient preference or whether patients understood the discussion. In summary, improving surgical decision making so that it is oriented toward the outcomes that patients value most should have a significant impact on decreasing inappropriate surgical care.

The reported incidence of poor surgical decision-making ranges from 15-50%. Postoperative studies in general and orthopedic surgery populations testing patients' knowledge of risks of surgery after signing informed consent paperwork have generally found understanding to be poor. Approximately 50% and 42% respectively were unable to name any potential complications. Analysis of data regarding medical decision making during office visits showed that fewer than 10% fulfilled minimum standards for informed decision making.[47] These studies are limited because they address only a few specific procedures, have small sample sizes, and are of inadequate scope to elucidate the reasons for low quality decision making. In the absence of available data, it is difficult for clinicians, consumers or payers to determine the quality of decisions made about most common medical tests and treatments.

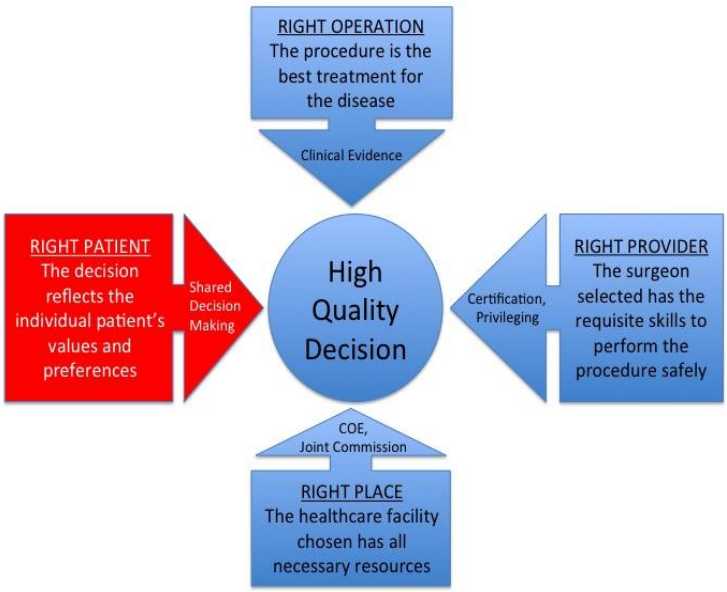
Preliminary studies by our research team

Our pilot data showed that about 13% of patients exhibited deficits in their informed consent process before surgery, and over 33% exhibited other types of deficits.[48] Informed consent deficits refer to not knowing the procedure being performed or the risks and benefits of the procedure. Other deficits related to not having addressed patient values, preferences and goals. For example, 11% of patients expressed doubts about whether in fact they wanted to undergo surgery at all, 76% had not completed advanced directives, and 25% of patients reported that they would have benefited from further discussion.[48] Non-English language and lower educational level were suggestive of higher risk for these deficits. Also, because those scheduled for the intensive care unit postoperatively seemed to be at higher risk of deficits, we have undertaken additional projects to improve communication and concordance in medical decisions for high-risk surgical patients. This includes a grant funded by FAER to develop a training program for communicating with patients who are having surgery and have a DNR order. The purpose is to elicit patient expectations, preferences, goals and values around postoperative care and use of life-sustaining therapy to should they be required to make decisions in the postoperative period.

A recent review outlined the historical approaches to ensuring appropriateness in surgery, and noted that the absence of concordance with patient values and preferences may not be considered sufficiently.[49] In addition, we have reported that within our normal preoperative clinic structure, there are patients who are considered inappropriate for surgery for nonmedical as well as medical reasons.[50] Some of these patients were referred to palliative care.

SUMMARY

A consideration of patient indications for surgery must be assessed in the context of complete assessment of comorbidities as well as concordance with patient values and preferences (figure below). Ongoing work is needed to develop frameworks to ensure that these conversations occur.



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ANESTHESIOLOGY 2017
BOSTON OCTOBER 21-25

Cesarean Delivery Pain Management for the Breastfeeding Mother

Brendan Carvalho **Stanford University, California**

Lecture Synopsis:
The lecture summarizes various multi-modal analgesic options to optimize pain management after cesarean delivery (CD), specifically the role of neuraxial opioids, non-steroidal anti-inflammatories (NSAIDs), acetaminophen, dexamethasone, gabapentin, ketamine, wound infiltration, transversus abdominis plane (TAP) block. Analgesic drug exposure in breastfeeding neonates, and techniques to minimize the transfer of analgesics into breast milk will be considered. Patient-centered pain management options will also be discussed.

Introduction:
Pain associated with CD is the most important concern for expectant mothers (Table 1),[1] and is often incompletely relieved by pain management protocols. Pain after CD is described as moderate to severe, and equivalent to that after abdominal hysterectomy.[2] Postoperative pain goals proposed by the Joint Commission (pain scores of consistently <3 out of 10),[3] are infrequently attained after CD.[4] Good post-CD analgesia improves maternal functional ability, enhances recovery, improves interaction with newborn infants, and decreases likelihood of persistent opioid use.[5,6]

Outcome	Rank†	Relative Value‡
Pain during cesarean	8.4 ± 2.2	27 ± 18
Pain after cesarean	8.3 ± 1.8	18 ± 10
Vomiting	7.8 ± 1.5	12 ± 7
Nausea	6.8 ± 1.7	11 ± 7
Cramping	6.0 ± 1.9	10 ± 8
Itching	5.6 ± 2.1	9 ± 8
Shivering	4.6 ± 1.7	6 ± 6
Anxiety	4.1 ± 1.9	5 ± 4
Somnolence	2.9 ± 1.4	3 ± 3

Table 1: Patient preferences for anesthesia outcomes prior to cesarean delivery[3]

Data are mean ± standard deviation; †Rank = 1 to 10 from most (1) to least desirable (10) outcome; ‡ Relative value = dollar value patients would pay to avoid outcome (e.g., pay $18 of a theoretical $100 to avoid postoperative pain).

Neuraxial Opioids:
In the United States, most CD are performed with neuraxial anesthesia (spinal, epidural, or combined spinal-epidural techniques),[7] with the vast majority performed with spinal anesthesia.[8] Neuraxial opioids provide superior postoperative pain relief compared to intravenous opioids,[9,10] and is recommended by the American Society of Anesthesiologist's Obstetric Anesthesia and American Pain Society's Clinical Practice Guidelines practice guidelines.[11,12]

Neuraxial morphine is currently the "gold-standard" single-dose neuraxial post-CD opioid and provides effective and prolonged analgesia. The duration of post-CD analgesia after intrathecal (IT) or epidural morphine is 14-36 hours,[10,13-15] and is dose dependent. Time to first request for additional analgesia of 9.7-26.6 hours for IT morphine doses of 50-100 mcg versus 13.8-39.5 hours for doses >100-250 mcg.[15]
Intrathecal vs. epidural morphine: Both IT and epidural administration provide similar efficacy and duration of post-CD analgesia.[16,17] However, IT morphine is considered the preferred route because of a faster onset of analgesia, and requires a smaller dose with potentially less neonatal effects.
Optimal neuraxial morphine dosing: Optimal dosing is difficult to determine because of variability in patient response to neuraxial opioids. Neuraxial morphine appears to have an analgesic ceiling (50-200 mcg intrathecally[18] and 2-4 mg epidurally[19]). Larger doses may increase side effects without providing significant additional analgesic benefit. Patients experience a lower incidence of nausea/vomiting (OR 0.44) and pruritus (OR 0.34) when receiving lower (50-100 mcg) versus higher (>100-250 mcg) IT morphine doses for CD.

Lipophilic opioids (e.g., IT fentanyl and sufentanil) improve intraoperative analgesia (especially during uterine exteriorization). Lipophilic opioids have a very quick onset, whereas neuraxial morphine requires 45-60 minutes to achieve peak effect. IT fentanyl or sufentanil reduce intraoperative nausea and vomiting, decrease local anesthetic

requirements (less hypotension), and provide a better postoperative transition to other pain medications during recovery from neuraxial anesthesia.[20-22] However IT fentanyl 10-50 mcg provides limited post-CD analgesia, with a median analgesic duration of 2-4 hours.[13,14] A combination of a quick-acting lipophilic IT opioid (e.g., fentanyl 10-20 mcg) with a long-acting hydrophilic opioid (e.g., morphine 100-200 mcg) is commonly utilized,[8] with the aim of optimizing both intraoperative and postoperative analgesia.

Hydromorphone has an intermediate lipid solubility (between that of morphine and fentanyl). The analgesia and side effects with hydromorphone is similar to that observed with morphine;[23,24] although its onset is quicker and duration is slightly shorter.[25,26] The dose ratio of IT morphine to IT hydromorphone in the post-CD setting is 2:1.[24]

Continuous or patient-controlled epidural analgesia (PCEA) with neuraxial opioids such as fentanyl, sufentanil, hydromorphone, meperidine ± local analgesics has been used with some success after CD.[27,28] However, these catheter-based analgesic techniques decrease maternal mobility, increase nursing workload, may increase catheter-related complications (e.g., hematoma, infection) and add additional costs in comparison with single-dose neuraxial morphine.[29] PCEA may be worthwhile for patients with high postoperative analgesic requirements (e.g., chronic pain sufferers). No consensus currently exists regarding optimal continuous epidural or PCEA regimens.

Maternal and neonatal side effects: All opioids have the potential for placental transfer and therefore it is preferable to utilize small IT doses or to administer epidural opioids after cord clamping. Although neuraxial opioids provide superior post-operative analgesia compared to systemic opioids, certain maternal opioid-related side effects (such as pruritus) may be more frequent.[30,31] However, patients prior to CD rank pain relief above side effects such as nausea, vomiting or pruritus (Table 1).[1] Prophylactic metoclopramide and 5-HT_3 receptor antagonists reduce the incidence of postoperative nausea and vomiting and the need for rescue antiemetic treatment in women receiving IT opioids for CD.[32,33] Combination regimens may be more effective than individual antiemetic agents in treating nausea and vomiting. Opioid antagonists particularly nalbuphine 2.5 to 5 mg are considered first choice measure for managing opioid-related pruritus.[34] Antihistamines are less effective than the opioid antagonists.[35] 5-HT_3 receptor antagonists may be useful prophylaxis for neuraxial opioid-induced pruritus after CD.[36] The analgesic benefits derived from small doses of neuraxial opioids outweigh the rare risk of associated respiratory depression.[37,38]

Multimodal Analgesics:
There is over-reliance on opioids for the management of post-operative pain. Although neuraxial analgesia offers excellent postoperative analgesia, the majority of women will require additional analgesics after CD. Multimodal analgesic approaches should be used to augment the analgesic effects of neuraxial opioids.[39,40]

NSAIDs: A number of studies have shown NSAIDs are very effective for post-CD pain, especially in relieving visceral cramping pain.[41] The pain relief numbers needed to treat (NNT) for NSAIDs range from 1.8-2.7. NSAIDs also reduce the need for opioid analgesics by 30-50%,[42,43] and decrease opioid-related side-effects (such as nausea, pruritus, sedation).[44] There are no comparative studies between various NSAIDs in the post-CD setting, and selection should be based on hospital availability and breast-feeding compatibility.
COX-2 inhibitors (e.g., celecoxib) have been shown to be effective perioperative analgesics with pain relief NNT of 4.2 (200 mg) and 2.5 (400 mg).[45,46] Although there are potential advantages in using COX-2 inhibitors in this setting (no effect on platelet function, less risk of bleeding), the routine use of these drugs is not currently recommended because studies evaluating the drug's use for CD showed limited analgesic benefit.[47-49] In patients that are intolerant of NSAIDs, celecoxib can be considered.[49]

Acetaminophen is an effective analgesic with a 20% opioid-sparing effect.[50] Around-the-clock scheduled acetaminophen rather than combination opioid/acetaminophen pills is preferable to minimize opioid use and avoid exceeding recommended maximum daily acetaminophen doses of 3,250 mg.[51] Intravenous acetaminophen preparations are useful in women unable to take oral medications, but should not replace oral formulations given the higher cost and lack of clear evidence for improved analgesia.[52] Acetaminophen and NSAIDs have an additive effect when used together for post-CD analgesia. [53,54] and therefore scheduled acetaminophen *and* NSAIDs for 2-3 days after CD is recommended.

Gabapentin and pregabalin have been shown to be useful perioperative analgesics and to have an opioid-sparing effect in the acute postoperative period.[55,56] In the CD setting, gabapentin (single dose 300 or 600 mg after delivery or a 2-3 day course) has shown limited analgesic efficacy.[57-59] The high umbilical vein to maternal vein ratio (0.86), potential breast milk transfer and sedation limits routine gabapentin use as a pre-emptive and post-operative drug in the CD setting.[57,60] In selected patients with pain that is difficult to manage, gabapentin may be a suitable analgesic.

Ketamine: Sub-anesthetic doses (10-15 mg) of IV ketamine have been shown to reduce opioid use for 24 hours after general surgery.[61] Analgesic benefit has been demonstrated after CD under general anesthesia, however limited analgesic efficacy was reported with ketamine 10 mg IV after CD with neuraxial opioids and multimodal postoperative analgesia.[62] Ketamine may be better suited in selected patients with increased pain management needs.

Dexamethasone in a single perioperative doses ranging from 1.25 to 20 mg has been shown to decrease post-operative pain, reduce opioid consumption and decrease postoperative nausea and vomiting without increasing wound infection or healing.[63-65]

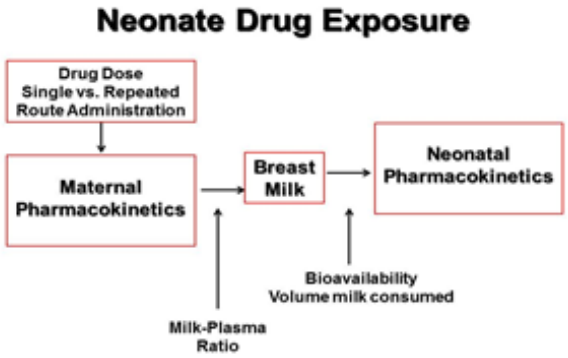
Intrathecal and epidural adjuncts (e.g., clonidine, neostigmine) do not appear to offer substantial improvement in acute postoperative pain over that of neuraxial opioids. Many of these neuraxial adjuvants are also associated with side-effects that has limited the routine use of these drugs.[66] However, these drugs may decrease pain sensitization and therefore may have a role in reducing persistent post-operative pain.[67]

Local anesthetics:
Wound infiltration: Studies investigating the analgesic benefit of local anesthetic wound infiltration in the obstetric populations have shown mixed results, and the analgesic effect is generally limited to the early post-operative period following general anesthesia.[68] Single-dose wound infiltration at the time of surgery is not usually effective following spinal anesthesia since the local anesthetic effect may not last beyond the duration of the neuraxial anesthesia (especially if an IT opioid is added).
A continuous irrigation of local anesthetic into the wound can prolong analgesia and decrease opioid consumption for 48 hour post-CD.[68-70] If continuous irrigation of local anesthetic is utilized, sub-fascial insertion of the wound catheter appears more effective than subcutaneous placement.[71] Continuous irrigation of local analgesia into the wound has been proposed as an alternative to an epidural technique,[72] however analgesic efficacy is limited to incisional analgesia and reliability is variable.[68,69] Neuraxial opioids provide incisional and visceral analgesia, and are particularly effective after abdominal surgery.[73] Local anesthetic infiltration or irrigation techniques should be considered as adjuvants for and not as replacements for neuraxial opioids or NSAIDs.
Incisional wound administration of drugs other than local anesthetics such as diclofenac, ketorolac, dexamethasone and opioids, have been demonstrated analgesic benefits post-CD.[74,75] Once the biological implications of wound administration are better understood, wound administration of adjuvant drugs may become a valuable analgesic alternative to systemic administration but with less potential side effects.

Transversus abdominis plane (TAP) block decreases pain and analgesic consumption in women who undergo CD under general anesthesia, and spinal anesthesia without IT morphine, however minimal additional analgesic benefit has been found with TAP blocks in women already receiving IT morphine with multimodal analgesia.[76,77] TAP blocks in this setting are usually performed after skin closure prior to transfer to recovery. Another proposed indication for TAP blocks for CD is for rescue analgesia to manage breakthrough pain after offset of spinal anesthesia, and to reduce the need for escalating opioid doses (with its associated side effects) following cesarean delivery.[78] Differentiation between somatic incisional and visceral cramping pain is important before offering TAP blocks since this technique is likely only effective for incisional pain. The duration of analgesia after TAP blocks with a single dose of ropivacaine or bupivacaine is limited to 8-12 hours.[79] Studies comparing TAP blocks to IT morphine have found that IT morphine provides better analgesia but more opioid-related side effects. [76,77] High local anesthetic blood concentrations are reported after TAP blocks,[80] and several cases of local anesthetic toxicity have been reported in this setting.[81,82] A case series suggests a role for continuous TAP block following CD.[83] Adjuvants such a clonidine, sufentanil and fentanyl offer limited additional analgesic benefit beyond the local anesthetic used for TAP block.[84] Quadratus lumborum block after CD with spinal anesthesia (without IT morphine) has been found to reduce opioid requirements and pain scores.[85]

Breastfeeding Considerations:
The vast majority of women in the United States attempt breastfeeding in the early postpartum period.[86] Neonatal drug exposure depends on a number of maternal, drug and neonatal factors (Figure 1). A relative infant dose (RID) >10% is generally considered a level of concern.[87,88] Most post-operative analgesics are fortunately well below this level (Table 2).

Table 2: Analgesics	Relative Infant Dose (RID, %)
Acetaminophen	1.3-6.4
Ibuprofen	0.1-0.7
Ketorolac	0.2-0.4
Celecoxib	0.3
Dexamethasone	No data
Gabapentin	1.3-6.5
Hydrocodone	1.6-3.7
Oxycodone	1.5-8
Tramadol	2.4-2.9
Fentanyl	0.9-3
Morphine	5.8-10.7



Neonatal drug exposure can be minimized by: utilizing the lowest effective maternal drug dose; using the most effective route of administration (IT vs. IV or oral opioids); understanding breastfeeding physiology and drug transfer (avoiding breastfeeding at peak drug concentrations or breastfeeding before drug administration); selecting drugs with low breast milk transfer, short half-life, inactive metabolites and a long safety record in this setting. All opioids enter the breast milk, transfer to the feeding infant, and may cause neonatal sedation and opioid-related side-effects. Fentanyl exhibits low breast milk transfer (RID 0.9-1.7%), has a short half-life and is rapidly redistributed, and is a preferred IV opioid in the breastfeeding setting.[89,90] Morphine has a low oral bioavailability that limits neonatal exposure.[91] Meperidine is metabolized to active normeperidine with a very long half-life (t ½±70 h) and is associated with neurobehavioral effects. Meperidine is best limited to small doses (e.g., 10-25 mg for shivering) in this setting.[89] Oxycodone and hydrocodone have been used extensively in nursing women with no reports of significant adverse effects to breastfed neonates, and are a better oral opioid than codeine after CD.[89,92] Due to their large molecular size and high degree of protein binding, there is minimal transfer of NSAIDs to breastfed neonates compared to opioids. The American Academy of Pediatrics and Academy of Breastfeeding Medicine considers most NSAIDs compatible with nursing mothers.[89,90] NSAIDs with short half-lives, long history of safe use, and minimal breast milk transfer such as ibuprofen (RID 0.1-0.7%, half-life of 2 hours) and ketorolac (RID 0.2-0.4%) are well-suited for breastfeeding women.[88,91,93] Celecoxib (a COX-2 inhibitor) also has minimal transfer to breast milk (RID 0.3%) and is considered safe if breastfeeding.[94] Acetaminophen is a drug with an excellent side-effect profile, a RID 1.3-6.4%, and no reported cases of neonatal harm. Acetaminophen is considered compatible with breastfeeding, although caution should be exercised in preterm neonates or neonates with liver dysfunction.[89,90] Gabapentin has a RID 1.3-6.5% and may result in sedation,[57,60] therefore caution should be exercised with the routine use of high-dose gabapentin. Local anesthetics result in very limited breast milk transfer; Ropivacaine (highly protein bound and very low breast milk transfer) is probably the best suited long-acting local anesthetic.[95]

Conclusions:
There is currently no analgesic "wonder drug" and post-CD pain must be managed using a multimodal analgesic approach as outlined by a suggested analgesic protocol (Table 3). Multimodal analgesia should include neuraxial morphine in conjunction with scheduled NSAIDs and acetaminophen should be administered in all appropriate women undergoing CD. The majority of women will require additional analgesics, and breakthrough pain is best managed with oral opioids (e.g., oxycodone, hydrocodone) while reserving IV opioids for severe or refractory pain. Local anesthetic wound instillation, TAP blocks, dexamethasone, gabapentin and ketamine are additional analgesic options in select patients or as rescue analgesia following CD (Table 3). In the future, standardized treatment plans

may be replaced with individual plans that utilize treatments tailored around specific patient needs.[96,97] Additional studies are needed to better understand the development of chronic pain after CD, and refine treatments that can reduce the occurrence of persistent incisional pain.[39]

Table 3:	Drug	Dose and Route	Prescribing Information
Routine care*	Neuraxial morphine	IT morphine 150 µg or Epidural morphine 3 mg	With IT hyperbaric bupivacaine 12 mg + fentanyl 15 µg
	NSAIDs	Ibuprofen 600 mg PO (or ketorolac 15 mg IV if NPO)	Every 6 h for 48–72 h
	Acetaminophen	Acetaminophen 650 mg PO (or IV if NPO/vomiting)	Every 6 h for 48–72 h
	Oral opioids	Oxycodone 5–10 mg PO	As needed for breakthrough pain
Ongoing or severe pain	IV opioids	IV morphine, fentanyl, or hydromorphone	Intermittent IV boluses or IV patient-controlled analgesia
	Regional anesthesia	Bilateral TAP block	0.25% ropivacaine 20–25 mL each side Single-shot ± catheter
	Oral adjuvants	Gabapentin	600 mg PO single dose (300 mg PO every 8 h for ongoing pain)
		Dexamethasone	4-8 mg IV single dose

*For women identified at risk for severe postoperative pain (e.g. chronic pain, opioid tolerant), consider postoperative patient-controlled epidural analgesia (with local anesthetic and opioid); or local anesthetic wound instillation (0.5% ropivacaine 5 mL/h subfascially for 48–72 h post-CD); dexamethasone 4-8 mg after delivery; or ketamine 10–15 mg IV after delivery of the baby.
Based on the analgesic protocol utilized at Lucile Packard Children's Hospital, Stanford University, California.

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Anesthesia Management of Emergency Endovascular Thrombectomy for Acute Ischemic Stroke

Bradley J. Hindman, M.D. **Iowa City, Iowa U.S.A.**

Introduction

From 2010 to the present, there have been numerous (n>21) observational *(non-randomized)* reports regarding the effect of anesthetic management on the functional outcome of patients undergoing emergency endovascular thrombectomy (EVT) to treat acute ischemic stroke. With some exceptions,[1-5] most observational reports suggest outcomes are more favorable when EVT is conducted with local anesthesia (with or without intravenous sedation—conscious sedation [CS]) instead of general anesthesia (GA). Based on these observational reports, at the present, the neurointerventional community generally favors the use of CS instead of GA for EVT.[6]

In early 2014, the Society for Neuroscience in Anesthesia and Critical Care (SNACC) published an expert consensus statement regarding anesthetic management of EVT.[7] The statement was based on a literature review through August, 2012, including five of the first observational reports.[8-12] Subsequently, in addition to many more observational reports, **three randomized clinical trials (RCTs) of CS *vs.* GA for EVT have been completed**, in order: SIESTA,[13,14] ANSTROKE,[15] and GOLIATH.[16,17] Thus, there is now a greater fund of evidence upon which to base decisions regarding the anesthetic management of patients undergoing EVT. Based on the three recent RCTs, **GA can now be considered to be a reasonable and safe choice for EVT patients.**

Endovascular Thrombectomy

In 2015, five RCTs established EVT using second generation thrombectomy devices (retrievable stents, called "stentrievers") and/or rapid workflow to decrease time to reperfusion significantly improves outcomes of patients with acute ischemic stroke due to large vessel thrombotic occlusion in the anterior circulation: MR CLEAN,[18] EXTEND-IA,[19] ESCAPE,[20] SWIFT-PRIME,[21] and REVASCAT.[22] In all five studies, compared with patients who received best medical therapy (usually tissue plasminogen activator [t-PA]), EVT nearly doubled the percentage of patients who recovered with little to no long-term (90 day) functional impairment, quantified as modified Rankin Scale (mRS) scores of 0, 1, or 2.

In the United States, EVT is currently performed in 129 medical centers designated by The Joint Commission as Comprehensive Stroke Centers (CSC).[23] At the present, 16 states do not have a CSC and 11 states have only 1 CSC. Criteria for a medical center to be designated as "thrombectomy-ready" have been proposed.[24,25] In addition to immediate availability of the complete range of acute stroke diagnostic and therapeutic specialists, "thrombectomy-ready" hospitals must have sufficient case volume (>30 EVT/year) and achieve EVT workflow targets: 1) time from CSC arrival to arterial puncture <90 minutes; 2) diagnostic imaging to arterial puncture <60 minutes; and 3) arterial puncture to first thrombectomy attempt <30 minutes,[24] or even faster.[6]

The emphasis on rapid workflow is because **the effectiveness of EVT progressively decreases as the interval between stroke onset and reperfusion increases**; there is no benefit unless reperfusion is established within 6-7 hours of stroke onset.[26] For example, among 390 patients who achieved substantial reperfusion with EVT, each hour reperfusion was delayed decreased the likelihood of functional independence, OR=0.85 (95%CI=0.77-0.95).[26] Thus, **EVT is truly an emergency procedure** and every minute counts.

A. Characteristics of EVT Patients

EVT patients present with signs and symptoms of acute ischemic stroke. The vessels most commonly occluded (~90%) are the large conducting arteries of the anterior cerebral circulation—the distal internal carotid artery (ICA) and/or one or more middle cerebral artery (MCA) branches. Approximately 10% of EVT patients will have an occlusion in the posterior (vertebrobasilar) circulation. Stroke severity is characterized by the NIH Stroke Scale (NIHSS), which ranges between 0 (no neurologic deficit) to a maximum value of 42. A patient with a complete hemiparesis, but with no other neurologic deficit, would have an NIHSS score of 8. By comparison, **EVT patients usually have NIHSS scores ≥15-20**,[18-22] which are considered to **be moderate-to-severe strokes**, with neurologic abnormalities in addition to hemiparesis. With NIHSS scores ≥15-20, swallowing dysfunction (**dysphagia**) is present in at least 30% of patients.[27-29] Especially when the patient is supine, dysphagia may cause airway obstruction (from secretions) and/or increase aspiration risk. Difficulty speaking on the basis of motor dysfunction **(dysarthria),** which commonly co-exists with dysphagia,[28, 30] is present in ~50% of EVT patients.[31] Central language dysfunction (**aphasia**) is present in ~50% of EVT patients.[8,31-33] Aphasia may be so severe that the patient cannot speak (expressive aphasia—cannot generate speech centrally, but can understand speech) and/or cannot understand speech (receptive aphasia) and, consequently, cannot follow commands. A **pathologic breathing**

pattern (*e.g.*, Cheyne-Strokes) is present in ~25% of acute stroke patients and is associated with dysphagia and greater NIHSS scores.[34]

EVT patients are typically **elderly**, with a mean age 66±13 years.[26] Most EVT patients have one or more **co-morbidities** including: 1) chronic hypertension (≥60%); 2) atrial fibrillation (≥33%); 3) diabetes mellitus (≥20%); 4) coronary artery disease (~25%); and/or 5) prior stroke (10-15%).[26] Most EVT patients will be at least moderately **hypertensive** at presentation. Systolic blood pressure (SBP) is typically 140-150 mmHg,[18,20,22] but SBPs in the 160-180's are common.[35] Mean arterial pressure (MAP) at presentation is typically 100-105 mmHg.[35-37] Mild **hyperglycemia** (glucose 135-145 mg/dL) is common.[26] The majority (>50%) of EVT patients will have received intravenous t-PA within a few minutes before EVT. Accordingly, the majority of EVT patients are **coagulopathic** when they arrive in the interventional suite.

With this constellation of acute on chronic illness, the great majority of EVT patients will qualify as American Society of Anesthesiologists (ASA) Physical Status Score of 3E or 4E.[3] Many EVT patients will not be able to rapidly or effectively communicate their pre-stroke medical history, allergies, medications, or even their fasting status. Hence, anesthetic management decisions are often made with minimal information and always made with minimal time; see *CS vs. GA Decision Making*, below.

B. The Procedure

Based on an imaging performed prior to the patient's arrival in the interventional suite, the neurointerventionalist will know which cerebral vessels are occluded and are to be reopened. The neurointerventionalist usually obtains arterial access *via* the patient's right femoral artery. An initial digital subtraction angiogram (DSA) is obtained to confirm the location of the occlusion(s). A DSA **"roadmap" is created**, allowing subsequent live fluoroscopic images to be superimposed on the "roadmap" to guide angiographic procedures. After the roadmap is obtained, movement of the patient's head and neck can misalign the roadmap with subsequent fluoroscopic images, making the roadmap inaccurate. An inaccurate roadmap may increase the risk of vessel injury (dissection, perforation) from angiographic devices and/or increase the time to perform the procedure. That is why **patient immobility during EVT is important**.

After the occlusion is angiographically confirmed, a large bore guide catheter or distal suction catheter is advanced as close as possible to the clot. Then, a soft microcatheter guidewire is advanced blindly through the body of the clot. A microcatheter is then advanced over the guidewire until the distal end of the microcatheter exits the clot and is positioned downstream in the lumen of affected artery. The guidewire is removed and another angiogram is obtained by injecting contrast through the microcatheter to confirm the distal end of the microcatheter is intraluminal and downstream of the clot. The strentriever is then advanced inside the microcatheter until the distal end of the strentriever is placed beyond the distal end of the microcatheter and clot. Then the microcatheter is withdrawn and the self-expanding strentriever deploys. As the strentriever expands against the vessel wall, the clot is trapped within the stent mesh and perfusion is restored. Thereafter, the strentriever is withdrawn, pulling the strentriever and the trapped clot into the cervical guide catheter or intracranial suction catheter. Withdrawing the strentriever places **traction on the affected cerebral artery, causing temporary pain (headache), which can be marked.** The strentriever procedure requires suction to temporarily reverse blood flow, preventing the clot from being washed out of the strentriever, resulting in distal emboli. Some new large bore catheters have such effective suction that they can sometimes be used on their own to aspirate clot without the need for a strentriever.[38] Typically one or two cycles of strentriever deployment/withdrawal are sufficient to remove the clot; rarely more than 3 cycles are needed. A final angiogram is performed to determine how well perfusion in the affected vessels has been restored. The degree of reperfusion is classified using the modified Thrombolysis in Cerebral Infarction (mTICI) perfusion scale. mTICI class 2b (>50% opacification of the cerebral vascular bed beyond the lesion) and class 3 (complete reperfusion) are considered to constitute adequate reperfusion. From arterial puncture to final angiogram, EVT takes about 60-90 minutes, although some recent trials report reperfusion within 30 minutes of arterial puncture.[39-41]

Stenting of a diseased ipsilateral internal carotid artery is sometimes performed in conjunction with EVT; 13% of patients in MR CLEAN,[18] 9% in REVASCT,[22] 19% in SIESTA,[14] and 24% in ANSTROKE.[15] These patients will need to receive intra-procedure antiplatelet agents (*e.g.*, tirofiban), further increasing their propensity to bleeding.

C. Determinants of EVT Effectiveness

A key determinant of EVT effectiveness is the **adequacy of collateral perfusion** to the ischemic brain prior to establishing reperfusion.[42,43] In MR CLEAN, EVT patients who had moderate to good collaterals (~66%) benefited from EVT, whereas patients with poor or absent collaterals (~33%) did not.[44] The most likely reason is

that good collaterals result in greater cerebral blood flow (CBF) to the ischemic penumbra,[45,46] and greater penumbral CBF slows the progression from cerebral ischemia to cerebral infarction.[47,48] Thus, good collaterals slow the rate of ischemic brain death, such that there is greater—*but not indefinite*—time to achieve reperfusion.

In the only study of its type, Olsen *et al.* showed CBF in the penumbra, which was supplied by collaterals, changed more in response to changes in systemic blood pressure than did CBF in normal (non-ischemic) brain.[49] Hence, at least in part, collateral flow to the penumbra depends on systemic blood pressure. Because collateral perfusion is so important, it follows that decreases in systemic blood pressure prior to reperfusion may be injurious. This has been confirmed in two recent observational studies. First, in a subset of 60 GA patients from the MR CLEAN trial, decreases in intraprocedure MAP were associated with less favorable outcome (mRS); per 10 mmHg decrease from baseline MAP (which was 100 mm Hg) OR=0.60 (95%CI=0.43-0.90); P=0.03.[36] In a different study by Whalin *et al*., all patients underwent EVT with CS (dexmedetomidine).[37] Patients presented with a MAP=107 mm Hg and functional outcome was associated with all indices of decreased MAP prior to reperfusion. Almost identical to the MR CLEAN results, a decrease in MAP below 100 mmHg decreased the likelihood of good outcome; per 10 mmHg decrease OR=0.78 (95%CI=0.62-0.99); P=0.043. Thus, **irrespective of anesthetic method, any substantive decrease in BP prior to reperfusion appears to be harmfu**l. Apparent outcome differences between CS and GA in some observational studies may be explained, at least in part, because of BP differences between CS and GA.[12,50] *In principle*, anesthetic management that prevents (or quickly reverses) decreases in blood pressure prior to reperfusion will facilitate more favorable outcomes; see *Randomized Clinical Trials of CS vs. GA for EVT,* below.

Another key determinant of EVT effectiveness is the **time between stroke onset and establishing reperfusion**. In MR CLEAN, both: 1) the likelihood of successful reperfusion; and 2) the likelihood of neurologic benefit following successful reperfusion decreased with increasing time.[51] There was no significant benefit when the interval from symptom onset to reperfusion exceeded 6 hours. In SWIFT-PRIME, the likelihood of functional independence was 91% if reperfusion was achieved within 150 minutes from symptom onset. The likelihood of good outcome decreased by ~10% (absolute) over the next 60 minutes, and then 20% (absolute) with every additional hour to restore perfusion.[39] Some, but not all, observational studies report GA delays the start and/or performance of EVT. In ESCAPE, in which only 9% of EVT patients received GA: 1) time between CT scan and arterial puncture was 22 minutes greater with GA (RR=1.43 [95%CI=1.05-1.93]); and 2) time between arterial puncture and reperfusion was slightly (~5 minutes), but not significantly, greater with GA (RR=1.15 [95%CI=0.77-1.70]).[40] In contrast, in SWIFT PRIME, in which 36% of EVT patients received GA, neither the time between CT scan and arterial puncture (median 52 minutes) nor the time between arterial puncture and reperfusion (median 32 minutes) were greater with GA; RR of 0.96 (95%CI=0.81-1.13) and 0.91 (95%CI=0.74-1.13), respectively.[39] *In principle*: 1) institutional workflow that routinely incorporates the anesthesia team; and 2) anesthetic management that minimizes the time required to start EVT will facilitate more favorable outcome; see *Randomized Clinical Trials of CS vs GA for EVT,* below.

Other important determinants of EVT outcome include: 1) **stroke severity** (NIHSS score) at presentation (greater NIHSS scores are associated with worse outcome);[52,53] 2) patient **age** (older patients have worse outcome);[52,53] 3) **occlusion location** (proximal arterial occlusions have worse outcomes);[53,54] and 4) **degree of reperfusion**.[53-55] Although not achieving statistical significance, many observational studies have reported greater rates of good (mTICI 2b/3) reperfusion with GA than with CS.[2,4,5, 56-59] *In principle*, the absence of patient movement during EVT may provide better conditions for the neurointerventionalist which may result in a greater technical success; see *Randomized Clinical Trials of CS vs. GA for EVT,* below.

Randomized Clinical Trials of Conscious Sedation (CS) *vs.* General Anesthesia (GA) for EVT

Three RCTs of CS vs. GA for EVT have been completed: SIESTA,[13,14] ANSTROKE,[15] and GOLIATH.[16,17] At the time this review is written (June, 2017), only some GOLIATH results are available in abstract form.[17] As summarized in Table 1., **all three trials found GA was <u>not</u> associated with less favorable 3-month outcomes**.

All three trials had similar intra-procedure blood pressure goals: SIESTA (systolic pressure=140-160 mm Hg); ANSTROKE (systolic pressure=140-180 mm Hg); and GOLIATH systolic pressure ≥140 mmHg and MAP≥70 mm Hg. **Almost all patients—*both CS and GA*—required vasopressors to maintain arterial pressure,** often at large doses; see Table 2. Nevertheless, in ANSTROKE, the percentage of patients who had >20% decrease in MAP at any time was greater in GA than in CS patients (41/45=93% *vs.* 26/45=60%, respectively; P=0.0003).[15]

Table 1. Functional Outcomes in RCTs of CS *vs.* GA for EVT

90 day Outcomes	Study	CS	GA	P Value
Good functional outcome (mRS ≤2)	SIESTA	14/77=18%	27/73=37%	P=0.01
	ANSTROKE	18/45=40%	19/45=42%	P=1.00
	GOLIATH*	33/63=52%	44/65=67%	P=0.08
Mortality	SIESTA	19/77=25%	18/73=25%	P>0.99
	ANSTROKE	11/45=24%	6/45=13%	P=0.28
	GOLIATH*	8/63=13%	5/65=8%	P=0.35

*GOLIATH values interpolated from graphs. P values (Pearson chi squared) calculated by this author.

Table 2. Anesthesia and Hemodynamics in RCTs of CS *vs.* GA for EVT

EVT Anesthesia Management	Study	CS	GA
Anesthetic Agents for Maintenance	SIESTA	Remifentanil: ~0.02 mcg/kg/min* +prn Propofol: ~5 mcg/kg/min*	Remifentanil: ~0.12 mcg/kg/min* + Propofol: ~50 mcg/kg/min*
	ANSTROKE	Remifentanil: TCI 1.0-1.3 ng/ml	Remifentanil: TCI 3-6 ng/ml +Sevoflurane: 0.6-0.7 MAC
	GOLIATH	Propofol: 17-33 mcg/kg/min	Remifentanil (not specified) + Propofol: 33-167 mcg/kg/min
BP during EVT (mmHg)	SIESTA	SBP_{MEAN}=147 (144-150) MAP_{MEAN} =104#	SBP_{MEAN}=145 (141-148) MAP_{MEAN}=100#
	ANSTROKE	MAP_{MEAN}=95±11 MAP, % of baseline=88±10%	MAP_{MEAN} =91±8 MAP, % of baseline=89±9%
Vasopressor Administration	SIESTA	Percent of patients not reported NE: ~0.025 mcg/kg/min*	Percent of patients not reported NE: ~0.10 mcg/kg/min*
	ANSTROKE	34/45=76% patients NE: 0.03-0.06 mcg/kg/min	43/45=96% patients NE : 0.05-0.125 mcg/kg/min)

Values are mean±SD or median (interquartile range)
TCI=target controlled infusion. MAC=minimum alveolar concentration. SBP=systolic blood pressure.
MAP=mean arterial pressure. NE=norepinephrine.
*Estimated average, calculated using data from two SIESTA pilot trial studies,[59,60] and patient weight of 70 kg.
#Estimate based on reported values for systolic and diastolic blood pressures.

As summarized in Table 3, in both SIESTA and ANSTROKE, GA appeared to increase the time between evaluation and arterial puncture by as much as 10 minutes, an interval consistent with the time required to induce GA and intubate the patient. However, after GA was induced, the time between arterial puncture and reperfusion tended to be less with GA (~18 minute less). Good reperfusion was slightly, but not significantly, greater with GA.

Table 3. Workflow and Reperfusion in RCTs of CS *vs.* GA for EVT

EVT Workflow and Reperfusion	Study	CS	GA	P Value
Door[a] or CT[b] to arterial puncture (min)	SIESTA[a]	66±20	76±29	0.03
	ANSTROKE[b]	91 (55-123)	92 (68-121)	0.94
Duration of EVT (min)	SIESTA	130±63	112±63	0.04
	ANSTROKE*	74 (37-104)	55 (38-110)	0.66
Stroke onset to reperfusion (min)	SIESTA	Not reported	Not reported	
	ANSTROKE	250 (213-316)	254 (206-373)	0.78
Good perfusion (mTICI 2b/3)	SIESTA	62/77=81%	65/73=89%	0.67
	ANSTROKE	40/45=89%	41/45=91%	1.00

Values are mean±SD or median (interquartile range)
*Arterial puncture to reperfusion.

As summarized in Table 4, in both SIESTA and ANSTROKE**, a substantive fraction (9-33%) of CS patients had problematic movement during EVT. In both trials, 15% of CS patients required conversion to GA during EVT.** In SIESTA, CS-to-GA conversions were because of patient agitation (7/11=64%) and

respiratory/airway problems (3/11=27%). In ANSTROKE, CS-to-GA conversions were because of patient movement (2/7=29%) and airway problems (1/7=14%). In GOLIATH, CS-to-GA conversion was less frequent (4/63=6%). Why CS in GOLIATH was apparently more successful than in the other two trials is not clear at this time. It is also not clear why, in SIESTA, GA was associated with such a high rate of delayed extubation when compared to ANSTROKE (49% *vs.* 7%, respectively).

Table 4. Problems and Complications in RCTs of CS *vs.* GA for EVT

Problems and Complications	Study	CS	GA	P Value
Problematic patient movement during the procedure	SIESTA	7/77=9%	0/73=0%	0.008
	ANSTROKE	15/45=33%	0/45=0%	<0.0001
Intracranial vessel perforation or other catheter problem	SIESTA	2/77=3%	2/73=3%	0.96
	ANSTROKE	1/45=2%	3/45=7%	0.31
CS-to-GA conversion	SIESTA	11/77=14%	-	-
	ANSTROKE	7/45=16%	-	-
	GOLIATH	4/63=6%	-	-
Delayed extubation	SIESTA*	5/77=6%	36/73=49%	<0.001
	ANSTROKE#	3/45=7%	3/45=7%	1.00
Pneumonia	SIESTA	3/77=4%	10/73=14%	0.03
	ANSTROKE	7/45=16%	6/45=13%	1.00

*Still intubated 2 hours after end of EVT; 5 of 11 CS patients who required CS-to-GA conversion.
Extubated after leaving the interventional suite; 3 of 7 CS patients who required CS-to-GA conversion.

Collectively, SIESTA, ANSTROKE, and GOLIATH demonstrate that **when: 1) GA is integrated into the standard workflow of EVT patients; and 2) blood pressure in GA patients is maintained at levels comparable to patients receiving CS (and, in both, at levels only slightly less [≤10%] than pre-EVT values), GA does not result in less favorable outcomes than CS.** Accordingly, anesthesiologists and neurointerventionalists can now decide to use GA when conditions require it with less concern that the patient will necessarily be adversely affected.

CS *vs.* GA Decision Making

In observational studies, approximately 10% of all EVT patients were intubated prior to EVT because of severe obtundation (GCS ≤8-9), overt respiratory failure, and/or increased intracranial pressure, *etc.*[1,50,56-58, 60,62,63] The need for intubation prior to EVT is associated with much less favorable outcomes.[57] Apparent outcome differences between CS and GA in some observational studies may be explained, at least in part, because all patients who were intubated prior to EVT were categorized as receiving GA.

The decision to be made is **who among the non-intubated EVT patients should receive CS and who should receive GA?** This decision will need to be made very quickly, within 1-2 minutes after the patient arrives to the interventional suite. Key assessments may include: 1) is the patient responsive to verbal or tactile stimuli; 2) can the patient lie supine without respiratory difficulty, either from airway obstruction, secretions (dysphagia) or a pathologic breathing pattern; 3) does the patient have acceptable oxygen saturation (>94-95%) with or without supplemental oxygen (nasal cannula or face mask); 4) can the patient understand and follow verbal commands (close eyes, open mouth, squeeze hand, and lie still); 5) if CS-to-GA conversion were to be needed, can the patient's airway be managed safety under non-ideal conditions. If the answer to any of these five items is "no," then greater consideration should be given to GA

In SIESTA, eligible consenting EVT patients were excluded prior to randomization because of "severe agitation" (42/245=17%) or vomiting (7/245=3%).[14] In ANSTROKE, eligible consenting patients were excluded from randomization when the anesthesiologist judged them to either: 1) *require GA* (38/208=18%, because of vomiting, agitation, inability to follow commands); or 2) *require CS* (21/208=10%, because of respiratory and circulatory comorbidities).[15] Thus, in both SIESTA and ANSTROKE, prior to starting the procedure, ~20% of EVT patients demonstrated either problematic agitation, inability to follow commands, or active vomiting, such that the need for intubation and GA was apparent prior to starting the procedure. Twenty percent may be an approximate lower limit for the percentage of EVT patients who would be expected to need GA.

In observational studies, it appears the great majority (>50%) of EVT patients can successfully undergo the procedure with CS. In ESCAPE[20] and REVASCAT,[22] CS was used in 91% and 93% of the patients, respectively. Ninety percent may be the approximate upper limit for the percentage of EVT patients who can undergo EVT with CS. As noted above, in ANSTROKE, approximately 10% of EVT patients had such severe comorbidity that CS was

considered by the anesthesiologist to be the safer than GA.[15] In this author's opinion, in the absence of strong indication for either CS or GA from the anesthesiologist's perspective, the recommendation of the neurointerventionalist should be favorably considered and utilized if possible. For a given patient, the neurointerventionalist may know the clot will likely be easy to retrieve and the procedure will likely be brief (30 minutes)—this favors selecting CS. Conversely, the neurointerventionalist may know the clot will be more difficult and/or there is severe carotid disease such that EVT will take more time and be more difficult—this favors GA. In addition, each neurointerventionalist will have their individual tolerance for patient movement during the procedure. In this author's opinion, in the absence of an indication (anesthesiologist) or recommendation (neurointerventionalist) for either GA or CS, CS should probably be the default method.

CS and GA Methods

At the present, when GA is selected, there is not sufficient clinical evidence to support the use of one general anesthetic agent (or agents) *vs.* any other. Regardless of primary method of GA**, a proactive and intensive approach toward maintaining the patient's blood pressure at the level present prior to EVT appears to be essential for GA to be conducted safely**. At the present, there is not sufficient clinical evidence to support the use of a specific vasoactive agent to support blood pressure during EVT. A single observational study of GA patients reported end-tidal carbon dioxide values were less in patients with unfavorable *vs.* favorable outcome; 32 *vs.* 35 mmHg, respectively, P=0.03.[64] Although this observation must be interpreted with great caution, hyperventilation (hypocarbia) is not likely to benefit EVT patients. Conversely, the effect of hypercarbia has not been formally studied in EVT patients. However, approximately 10% of acute stroke patients show evidence of decreased CBF in the affected vascular territory with 15-30 seconds of breath-holding.[65] This is thought to be due to hypercarbia-induced CBF redistribution away from penumbral tissue ("steal"), and CO_2-induced steal physiology been observed in patients with chronic (non-acute) intracranial occlusive disease.[66] Thus, at the present, maintenance of **arterial normocarbia during GA appears to be advisable**. GA techniques that increase the likelihood of immediate emergence and optimal conditions for extubation at the end of EVT would also seem advisable.

At the present, when CS is selected, there is not sufficient clinical evidence to support the use of one sedative, hypnotic, or analgesic *vs.* any other. Observational studies that have utilized primarily dexmedetomidine [1,37,67] and propofol[67] show both agents can result in: 1) substantive decreases in blood pressure; and 2) the frequent need for vasopressors. Even small intermittent doses of midazolam and fentanyl can often cause relatively large decreases in blood pressure and the need for pressors.[5] Thus, just like with GA, **a proactive and intensive approach toward maintaining patient blood pressure is an essential aspect of CS**. However, accomplishing this goal may be somewhat easier with CS than with GA.[1,5,14,15,50] At the present, there is not sufficient clinical evidence to indicate one agent is superior to another in minimizing the need for CS-to-GA conversion.

When reperfusion is restored (or the neurointerventionalist determines additional procedures are not worthwhile), EVT is completed; only a few minutes are needed to remove the femoral arterial access catheter and manage the puncture site (manual compression or closure device). Although there is no direct evidence to prove it, some authors recommend **EVT patients who have good reperfusion (mTICI 2b/3) should have moderate blood pressure reductions (systolic pressure < 140 mmHg)** in an effort to decrease reperfusion-related adverse events (*e.g.*, hemorrhagic transformation and/or cerebral edema).[68-70] In contrast, for patients who are not well reperfused (mTICI 2a or less), hypertension (systolic pressure ≤180) may be maintained for at least another 24 hours to support collateral flow.[68,69] Hyperoxia may exacerbate reperfusion-related brain injury, and observational studies report intubated stroke patients who are hyperoxic have less favorable outcome.[71] However, with risk adjustment, the association is no longer significant.[72] Therefore, in EVT patients who have good reperfusion, consider decreasing inspired oxygen concentration to achieve arterial hemoglobin saturations in the 95-98% range, so long as doing so appears to otherwise be safe.

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U.S. Anesthesia Workforce and Group Practice Trends: Data Sources and Research Questions

Thomas R. Miller, PhD, MBA **Schaumburg, Illinois**

Background and Objectives

At the end of 1966, more than 50 years ago, there were 7,011 physician anesthesiologists in practice in the United States (U.S.); just over half (52.6%) were board certified.[1] In 1969, there were an estimated 10,500 professionally active nurse anesthetists and expectations of a long-term severe shortage of anesthesiologists.[1-2] However, some experts questioned how real the shortage might be and whether it could be avoided if current (*in 1969*) anesthesia professionals were better organized and more effective in meeting their productivity potential.[3] One of the first articles focusing on the U.S. anesthesia workforce was published in 1970 – a time when there were 200 residencies with 1500 residents, with half of the anesthesiology residents from non-US medical schools.[4]

Over the past 50 years, the growth and changes in the medical workforce have been substantial and often surprising to the "experts" who have attempted to predict future workforce needs, expected supply and the implications for education and practice. Predictions of shortages and surpluses have come and gone over time, focusing on both primary care and specialists.[5] In its February 2017 update, the Association of American Colleges (AAMC) projected a total physician shortfall of between 40,800 and 104,900 physicians by 2030; the shortfall for non-primary care specialties is projected to be between 33,500 and 61,800, and AAMC projected a shortfall of surgeons of between 19,800 and 29,000.[6] The majority of the AAMC report text described the complexities of physician supply and demand projections; it is a valuable reference for those researchers interested in studying workforce projections.

There are several data sources and supporting resources available for researchers interested in better understanding the medical workforce, and specifically interested in the demand for, and supply of, physician anesthesiologists, nurse anesthetists and anesthesiologist assistants. However, given the inherent differences among the data sources and the continuing changes in physician practice settings, care delivery models and organizational relationships, there is probably only one statement we can make with confidence: "*Every number reported is, in some way, incorrect!*"

There have been many assessments of the adequacy of the number of anesthesiologists and predictions for the specialty have varied in recent years.[7-13] The topic of workforce supply and demand is no doubt critical to any specialty; however, it is just one area of important research within the anesthesia workforce space; this Review Course Lecture discusses several other related research topics.

The learning objectives of this Review Course Lecture include to:(1) Identify sources for U.S. anesthesia workforce data and highlight their potential and limitations; (2) Separate popular declarations and myths from evidence-based trends concerning the anesthesia workforce, including group practice characteristics and geographic distribution of anesthesia professionals; and (3) Develop a short list of anesthesia workforce-related research questions to review or undertake.

Workforce Data Resources

There are several sources for workforce-related information, including:

- Accreditation Council for Graduate Medical Education (ACGME) Data Resource Book
  (http://www.acgme.org/About-Us/Publications-and-Resources/Graduate-Medical-Education-Data-Resource-Book)
- American Medical Association (AMA)
  (https://www.ama-assn.org/life-career/ama-physician-masterfile)
  (https://www.ama-assn.org/about-us/health-workforce-mapper)
- Association of American Medical Colleges (AAMC)
  (https://www.aamc.org/data/workforce/)
- Centers for Medicare and Medicaid Services
  (https://www.cms.gov/Research-Statistics-Data-and-Systems/Files-for-Order/LimitedDataSets/)
  (https://www.resdac.org/cms-data/files/md-ppas)
- *Marketing firms and other vendors*
  For example, SK&A (http://www.skainfo.com/databases#physicians)

- National Plan & Provider Enumeration System/National Provider Identifier (NPPES/NPI)
  (https://www.cms.gov/Regulations-and-Guidance/Administrative Simplification/NationalProvIdentStand/DataDissemination.html)
- National Resident Matching Program (NRMP) Match Data
  (http://www.nrmp.org/match-data/about-match-data/)
- Physician Compare National Downloadable File
  (https://data.medicare.gov/data/physician-compare)
- U.S. Bureau of Labor Statistics
  (https://www.bls.gov/oes/home.htm)

In addition to the above organizations that provide relevant workforce data, there are several health workforce centers located in universities across the US. These centers provide data and additional workforce research support services. Selected centers include:

- Center for Health Workforce Studies at the State University of New York at Albany (SUNY), School of Public Health
- Center of Excellence in Public Health Workforce Studies at the University of Michigan
- George Washington University Health Workforce Institute
- Health Research, Inc. at Center for Health Workforce Studies at the State University of New York at Albany
- Midwest Center for Health Workforce Studies at UIC Institute for Health Research and Policy
- Program on Health Workforce Research and Policy at University of North Carolina at Chapel Hill
- Regional Center for Health Workforce Studies at UT Health Science Center at San Antonio
- University of California at San Francisco Health Workforce Research center on Long-term Care
- University of Washington Center for Health Workforce Studies

How Many Anesthesia Professionals Are There?

Given the plethora of workforce data sources and resource centers, it seems it should be relatively easy to estimate the number of anesthesia professionals in the U.S. However, differences in the sources of the raw data, the definitions used, and the amount of primary data collection and data "cleaning" conducted all result in substantial differences in the estimates of anesthesia workforce supply.

Table 1 presents anesthesia workforce estimates from four sources; the variation in reported workforce size is substantial. Researchers should understand several key aspects of the workforce data to be used in any analysis:

- What is the specific origin of the data; (e.g., claims data, self-reported, or another source)?
- What are the available data items (variables) and their definitions (e.g., age, specialty, address)?
- Is level/type of activity included (e.g., research, teaching, patient care; full-time or part-time; retired or inactive)?
- Are residents and medical students included?
- What geographic data are included (e.g., U.S. territories)?
- How are the specialties defined? How many specialties can be listed for each physician?

For the data sources reported in Table 1, there are several important differences. Information in the national NPI dataset it typically input and updated by the provider. There is no indication as to the date of the most recent update for the provider's information. The provider's type and level of activity (e.g., research, teaching, patient care, full-time or part-time) are not provided. These data are commonly used in research.[14]

The AMA Master File data exclude non-physicians. The specialty and subspecialty designations are based on self-report. The total count of physician anesthesiologists in the AMA Master File, including those without NPIs, exceeds 63,000. It is likely that this estimate substantially overstates the actual number of physician anesthesiologists for several reasons.

The Physician Compare files include only those providers that have submitted a Medicare claim in the previous 12 months or have recently joined the Medicare roll as a provider. Pediatric anesthesiologists and other anesthesia professionals that do not accept Medicare are probably understated in these data.[15]

Finally, the Bureau of Labor Statistics (BLS) estimates do not include "self-employed workers." Therefore, the number of physician anesthesiologists reported by the BLS is substantially understated.

The above examples illustrate some of the more important differences; there are several others of which researchers should be aware.

Table 1. Number of U.S. anesthesia professionals reported from various data sources

Data Source	Physician Anesthesiologists	Nurse Anesthetists	Anesthesiologist Assistants
NPPES National NPI Dataset[1]	53,232	52,605	2208
AMA Master File[2]	46,253	n/a	n/a
AMA Master File[3]	52,545	n/a	n/a
Physician Compare National File[4]	37,933	40,073	1767
Physician Compare National File[5]	40,028	42,658	1872
Bureau of Labor Statistics[6]	30,190	39,860	n/a

[1]Based on listed primary specialty in the mid-month May 2017 National NPI Dataset.
[2]Physicians with a primary specialty of anesthesiology. The file contains another 10,494 physicians missing NPIs.
[3]Includes anesthesiology subspecialties (e.g., pediatrics, pain medicine, critical care, obstetrics). The file contains another 10,950 physicians missing NPIs.
[4]Physician Compare National Downloadable File, June 15, 2017.
[5]Combined Physician Compare files for June 16, 2016 and June 15, 2017.
[6]Estimates do NOT include self-employed workers. http://www.bls.gov/oes
NOTE: Calculations by the ASA Center for Anesthesia Workforce Studies based on the above data sources.

In addition to the number of anesthesia professionals, their geographic distribution is of research interest and of interest to policy makers. Figure 1 presents the distribution of physician anesthesiologists in the U.S. In general, the distribution reflects the U.S. population distribution. Other important workforce data include compensation, productivity, organizational relationships and employment models.

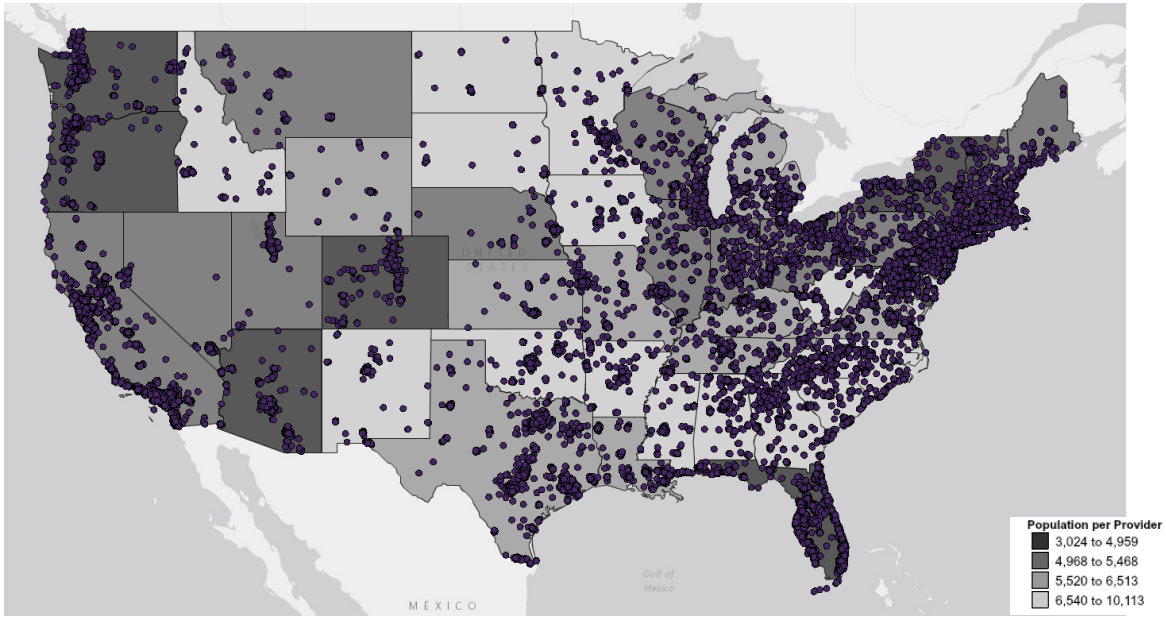

Figure 1. Geographic distribution of physician anesthesiologists in the continental U.S. Source notes: From the AMA Health Workforce Mapper based on the AMA Physician Masterfile 2013; Centers for Medicare and Medicaid Services' National Plan and Provider Enumeration System 2013; and U.S. Census county and states shapefiles 2010. Created by The Robert Graham Center for the ©American Medical Association. (https://www.ama-assn.org/about-us/health-workforce-mapper)

Anesthesia-related Group Practice Trends

Most physician anesthesiologists have seen the headlines or know first-hand about the acquisitions and growth in the physician group practice market; anesthesiology is one of the most active specialties in this arena. Haverford Healthcare Advisors identified 37 anesthesia-related group practice acquisitions in 2016.[16] The number of anesthesia practice acquisitions has increased each year since 2009, and the most acquisitions occurred in Florida, New Jersey, Texas and New York. The largest of the anesthesia-related group practice companies has more than 3,000 anesthesia providers.

Even a topic as seemingly well-defined as "anesthesia-related physician group practices" engenders complexities for the researcher. What minimum number of members constitutes a "group"? Is the measure based on all physicians, physician anesthesiologists, or all anesthesia professionals? What makes a large group practice large? Is it the total number of employed physicians, the number of all anesthesia professionals, the practice setting, the number of anesthetizing facilities served, the number of different states in which it operates? Should academic-based groups be considered differently from private or publicly-traded groups?

As of June 2017, only three publicly-traded group practice companies, in which anesthesia represents a substantial portion of the business, remain. Figure 2 presents the relative changes in the stock prices of these corporations along with the change in the S&P 600 Health Care Index Sector (S&P 600) between December 2, 2016 and June 15, 2017. EHC represents Envision Healthcare, Inc. and is the combined entities of AmSurg, Sheridan, and EmCare. MEDNAX includes Peidatrix Medical Group, American Anesthesiology, MedData, Surgical Directions, and VRad. CRH is a Canadian-based company focused on providing physicians with products and services for the treatment of gastrointestinal (GI) diseases, primarily in the U.S. CRH's first anesthesia acquisition was in the fourth quarter of 2014. By the end of 2016, CRH Anesthesia Management provided anesthesia services in 18 GI-focused ASCs, using a team of more than 50 nurse anesthetists under the supervision of an anesthesiologist medical director.

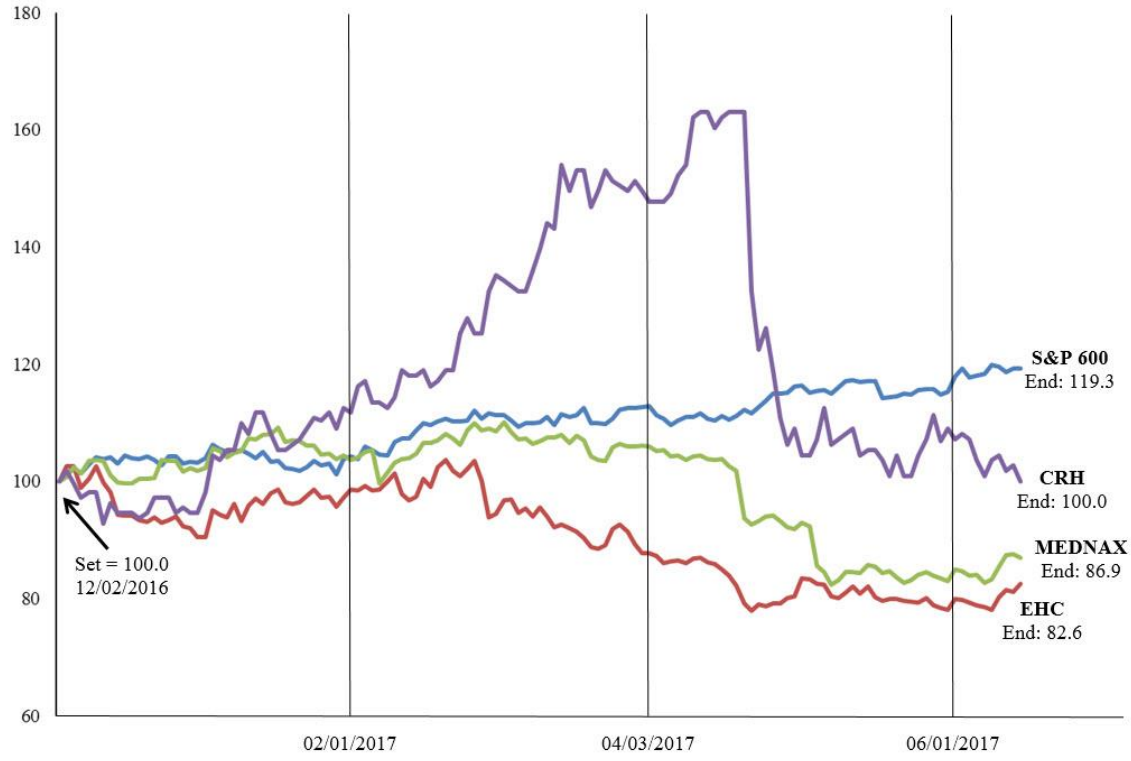

Figure 2. Relative changes in stock prices, 12/2/2016 – 6/14/2017 for Envision Healthcare Corporation (EHC), MEDNAX, Inc. (MEDNAX), CRH Medical Corporation (CRH), and the S&P 600 Health Care Index Sector (S&P 600). Calculations and graph by ASA's Center for Anesthesia Workforce Studies based on data from Yahoo Finance (https://finance.yahoo.com/) and Google Finance (https://www.google.com/finance).

Potential Research Questions

There are numerous opportunities for workforce-related research, fueled by anesthesia group practice trends, scope of practice regulations, and the evolution of payment and patient care delivery models. Potential research questions relevant to anesthesiologists and policymakers include:

- How many physician anesthesiologists, nurse anesthetists and anesthesiologist assistants are there in the U.S.? How has the changed over time?
- What is the geographic distribution of the anesthesia workforce and how has it changed over time? What are the implications for health policy?[17]
- What is the demographic profile of the anesthesia workforce and how has it changed over time? What are the implications of an aging workforce[18] and of a more diverse workforce?
- What are the trends in organizational and employment models among anesthesia professionals?
- What will be the demand for anesthesia services and professionals over the next 10 years? What are the implications of a shortage or surplus on educational need? What are the economic implications?
- What impact does the continued growth in anesthesia-related group practices have on the groups negotiating positions vis-à-vis payers and hospitals?[19]
- How much do changes in the supply of surgical and other specialties requiring anesthesia services have on the demand for anesthesia professionals?
- What impact do size and composition of anesthesia-related group practices have on quality of care?
- What are the future educational capacity needs for anesthesia and the implications for financing training programs?[20]

Conclusion

Anesthesia workforce data, projections of supply and demand, and related research are important to the specialty of anesthesiology. An understanding of anesthesia workforce trends and complexities is essential to inform health policy at the local, state and national levels. Workforce data are imperfect but improving; understanding the differences and definitions among the various information sources is a critical first step in any workforce-related research. Research gaps are substantial and more research efforts are needed to help define and describe the various characteristics of the workforce and to address critical health policy questions.

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Management of chronic pain in obese patients

Samer Narouze, MD, PhD

Definitions:

- Overweight is a body mass index (BMI) of 25 kg/m2 or greater but less than 30 kg/m2
- Obesity is a BMI greater than or equal to 30 kg/m2
- Extreme obesity is a BMI greater than or equal to 40 kg/m2.
- Abdominal obesity is waist circumference > 40 inches in men or > 35 inches in women. OR waist/hip ratio > 0.9 for men and > 0.85 for women

Prevalence of obesity:

Overweight/obesity is a global growing epidemic especially within the United States and Europe.[1,2]
Obesity is an expensive disease that is associated with significant disability.[3]
Obesity is the leading cause of preventable deaths and chronic disease.[4]

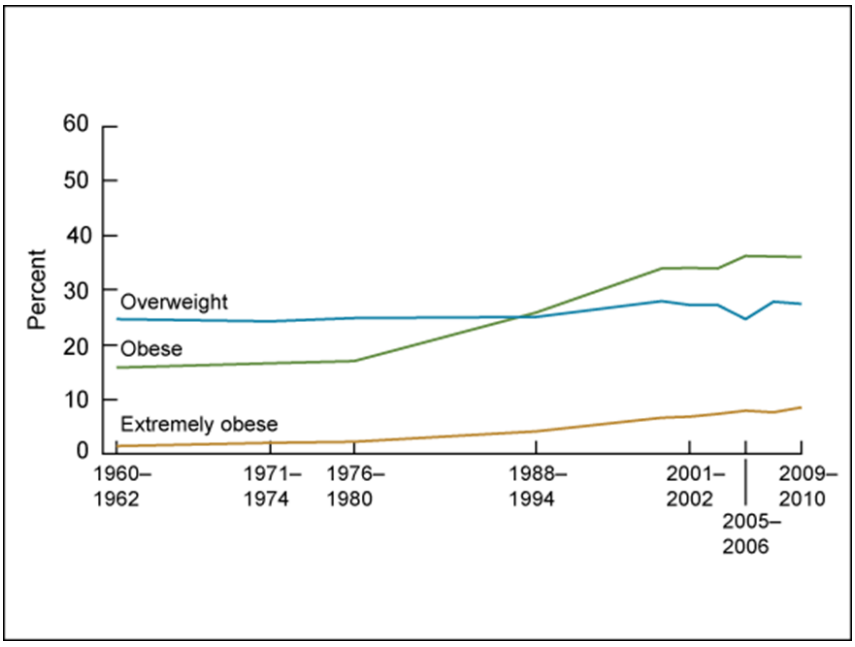

Figure 1:
Prevalence of obesity in USA[1]

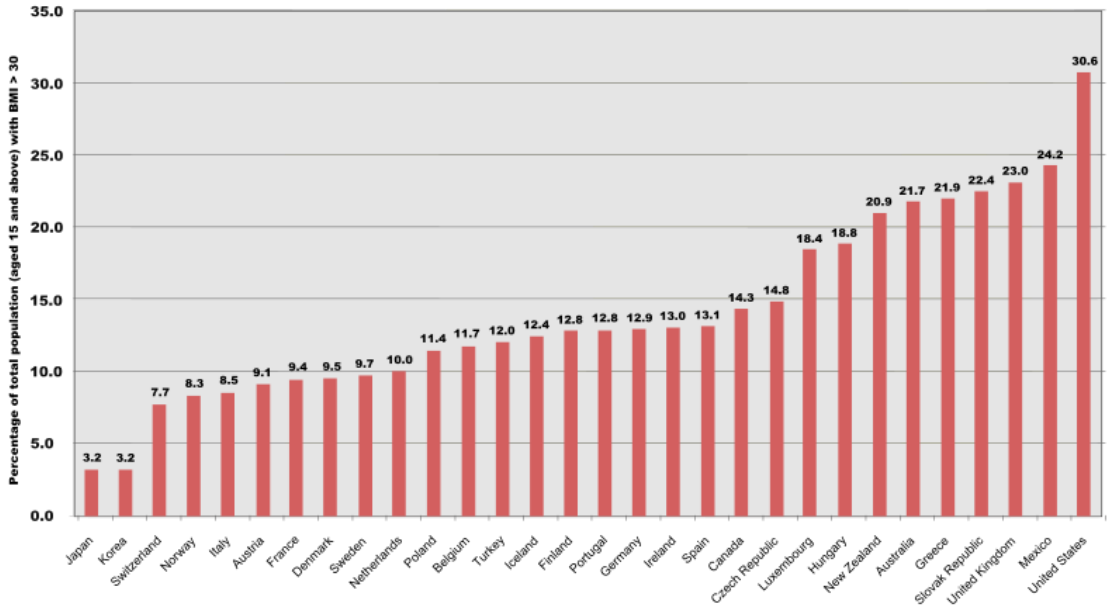

Figure 2:
Prevalence of obesity among different countries[2]

Obesity and low back pain:

Lifetime prevalence of LBP is estimated to be 70-85% with point prevalence rate around 30%.[5] Thirty-three studies were included in a recent meta-analysis that showed obesity was associated with increased prevalence of low back pain in the past 12 months, seeking care for low back pain, and chronic low back pain.[6] The results remained consistent after adjusting for publication bias and limiting the analyses to studies that controlled for potential confounders such as physical or psychosocial factors.
The association between obesity and the prevalence of low back pain is stronger for women than for men.

This gender-related difference can be explained by:

1- Hormone-related obesity and associated changes in pain sensitivity.[7]
2- Differences in the distribution of body fat mass or proportion of lean body mass (BMI). [8] In men, high BMI may reflect high muscle mass while in women, it may indicate amount of adipose tissue.

The majority of the reviewed studies were cross-sectional. Therefore, the association between obesity and low back pain could be bidirectional; that is, obesity may cause low back pain, or obesity can be a consequence of low back pain.[6]
Obesity is more likely in people who are sedentary during work or leisure activities. Low back pain could also lead to physical inactivity and hence to increased adiposity. Obesity and low back pain could also be comorbid conditions that share common risk factors.

Possible mechanisms for LBP in obesity:

1- Obesity can increase the mechanical load on the spine by causing a higher compressive force or increased shear on the lumbar spine structures during various activities.
2- Obese people may also be more liable to incur accidental injuries.[9]
3- Inflammatory effects of adiposity: Obesity may cause low back pain through systemic chronic inflammation. Obesity is associated with increased production of cytokines, acute-phase reactants and activation of pro-inflammatory pathways.[10] Obesity alone may increase one's risk for peripheral neuropathic disorders.[11]
4- Obese individuals were shown to be significantly more pain sensitive than non-obese. 12,13However, other studies in human and animal models have shown the opposite-decreased pain sensitivity in obese individuals.[14,15]
5- Abdominal obesity, hypertension and dyslipidemia (the metabolic syndrome) may be involved in the patho-mechanical pathway of low back pain.
6- Obesity is associated with disc degeneration. [16] Spinal mobility decreases with increasing body weight which may interfere with disc nutrition. [17]

Possible mediators and shared pathways between obesity and pain:

Sex
Age
Smoking
Diet
Physical activity
Socioeconomic and lifestyle factors
Height/stature
Distribution of body fat and waist circumference [18]

Low back pain and associations with body fat distribution and height:

Cross-sectional study in The Netherlands examined the associations of low back pain symptoms with waist circumference, height, waist to hip ratio and body mass index.
The prevalence of low back pain in men and women in the past 12 months were 46% and 52%,

Women who are overweight, or those with a predominant abdominal fat mass, indicated by large waist circumference, are at greatly increased risk of low back pain. Associations between anthropometric measures and low back pain are much weaker in men.[18]

Obesity and musculoskeletal pain:

- Osteoarthritis (OA) is the most common joint disorder, affecting more than 25 million Americans[19], and the leading cause of disability among older Americans.[20]

An Australian population-based research showed that the odds of hip and knee arthritis and OA was up to 7 times higher for obese individuals, compared with underweight/normal weight

individuals. Moreover obese individuals with arthritis or OA reported more pain, greater stiffness, worse function, and greater disease severity.[21]
Those who became overweight earlier in adulthood showed higher risks of lower limb OA. Waist/hip ratio (WHR) at time of examination did not associate with OA independently of BMI, except in women-only analysis. Waist circumference was associated with lower limb OA risk.[22]

- Obesity is a risk factor for fibromyalgia in adults [23] and musculoskeletal pain in adolescents.[24]

Obesity and migraine:

Obesity as a risk for chronic migraine. [25]
Obesity is an inflammatory state in which multiple pain-generating hormones are produced and released from fat cells, including calcitonin gene-related peptide, substance P, tumor necrosis factor-a, and interleukin-6. During a migraine, there is a similar release of these same pain-promoting hormones and neurochemicals.
Both gastric bypass and gastric lap banding show promise in reducing migraine frequency.[26]

Effect of Treatment on Pain and Weight Outcomes

- Lifestyle Intervention/Behavioral Weight-Loss Treatment

Lifestyle interventions encourage weight loss through diet, exercise, and behavior and thought modification.
The Arthritis, Diet, and Activity Promotion Trial (ADAPT) examined the effectiveness of exercise and dietary intervention on improving pain outcomes in overweight/obese older adults with knee OA. [27,28] Three hundred sixteen adults were randomized into diet only, exercise only, diet plus exercise, and healthy lifestyle (control) groups. Primary outcome variables included physical functioning, pain, and mobility.
Although the diet- only group experienced greater weight loss compared with the healthy lifestyle group, no pain-related improvement was evident. In the exercise-only group, the only significant improvement was in mobility. However, the diet and exercise group had significant improvement in physical functioning, self-reported pain, mobility, and weight.
Dietary modification coupled with exercise appears most effective in enhancing outcomes in nonsurgical interventions
There is little information on the prevention of low back pain with weight reduction via lifestyle modification.[6]

- Bariatric surgery appears to have a positive effect on pain outcomes.

Surgical intervention results in a greater reduction of musculoskeletal pain.[29]
Patients with lower-limb pain (e.g., foot, knee) reported significantly greater improvement in quality of life than those with LBP, often meeting or exceeding community norms.[30]

Results suggest that even modest weight loss may be beneficial and that the extent of weight loss is not necessarily predictive of enhanced pain outcomes.[31]
There is also preliminary evidence that weight reduction after bariatric surgery may result in recovery from low back pain. [32,33]

Does Obesity affect the treatment outcomes for LBP?

- Obesity was shown to affect outcomes following the treatment of symptomatic lumbar disc herniation.

An as-treated analysis was performed on patients enrolled in the Spine Patient Outcomes Research Trial (SPORT) for the treatment of lumbar disc herniation.[34]
At 4-year follow-up evaluation, improvements over baseline in primary outcome measures were significantly less for obese patients as compared with non-obese patients in both the operative treatment group and the non-operative treatment group. The benefit of surgery over non-operative treatment was not affected by body mass index.
Obese patients realized less clinical benefit from both operative and non-operative treatment of lumbar disc herniation. Surgery provided similar benefit over non-operative treatment in obese and non-obese patients

- Obesity was shown to affect outcomes following the treatment for lumbar stenosis (SpS) and degenerative spondylolisthesis (DS).

An as-treated analysis was performed on patients enrolled in the Spine Patient Outcomes Research Trial (SPORT) for the treatment of lumbar spinal stenosis (SpS) or degenerative spondylolisthesis (DS). [35]
At 4-year follow-up, operative and non-operative treatment provided improvement in all primary outcome measures over baseline in patients with BMI of less than 30 and 30 or more. For patients with SpS, there were no differences in the surgical complication or reoperation rates between groups. Patients with DS with BMI of 30 or more had a higher postoperative infection rate (5% vs. 1%) and twice the reoperation rate at 4-year follow-up (20% vs. 11%) than those with BMI of less than 30.
Obese patients had a significantly greater treatment effect than non-obese patients with SpS (Oswestry Disability Index, P = 0.037) and DS (SF-36 PF, P = 0.004) largely due to the relatively poor outcome of non-operative treatment in obese patients.
The authors concluded that; obesity does not affect the clinical outcome of operative treatment of SpS. There are higher rates of infection and reoperation and less improvement from baseline in the SF-36 physical function score in obese patients after surgery for DS. Non-operative treatment may not be as effective in obese patients with SpS or DS.

Opioids for chronic pain in obese patients:

The two most important factors that play an important role in prescribing opioids for chronic pain in obese patients are sleep apnea and risk for addiction.

Obesity and OSA:

- Obesity is considered a major risk factor for the development and progression of OSA.

The prevalence of OSA in obese or severely obese patients is nearly twice that of normal-weight adults. Furthermore, patients with mild OSA who gain 10% of their baseline weight are at a 6 fold increased risk of progression of OSA, and an equivalent weight loss can result in a more than 20% improvement in OSA severity.[36]

- The use of opioids has been associated with development of sleep-disordered breathing, including central apneas, nocturnal oxygen desaturations, and abnormal breathing patterns. [37]

Obesity and addiction:

Neuro-functioning imaging revealed the similarity and the overlapping brain circuits between obesity and drug addiction.
Drug addiction and obesity appear to share several properties. Both are disorders in which the saliency of a specific type of reward (food or drug) becomes exaggerated relative to, and at the expense of others rewards. Both drugs and food have powerful reinforcing effects, which are in part mediated by abrupt dopamine increases in the brain reward centers. [38,39]
Obese and drug-addicted individuals suffer from impairments in dopaminergic pathways that regulate neuronal systems associated not only with reward sensitivity and incentive motivation, but also with conditioning, self-control, stress reactivity and interoceptive awareness.

Recent advances in obesity treatment:

- Occipital Neuromodulation was shown to decreases body mass and modifies Autonomic Nervous System activity in morbidly obese patients.[40]

- A combination tablet was approved by the Food and Drug Administration in 2012 that contains phentermine and topiramate in a single tablet. This might prove helpful in preventing chronic migraines in obese patients.

- The Food and Drug Administration (FDA) in 12/2014 has approved Saxenda (liraglutide [rDNA origin]) injection as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients in the presence of at least one weight-related comorbid conditions.
  Saxenda is the first glucagon-like peptide-1 (GLP-1) receptor agonist approved for this indication. GLP-1 is a physiological regulator of appetite and calorie intake, and the GLP-1 receptor is present in several areas of the brain involved in appetite regulation.
  The approval was based on the Phase 3 SCALE (Satiety and Clinical Adiposity-Liraglutide Evidence in Non-diabetic and Diabetic adults) program that studied over 5,000 patients who are obese with comorbidities.

Study results showed that Saxenda, in combination with a reduced-calorie diet and increased physical activity, led to significantly greater weight loss vs. diet and physical activity alone.

- Vagal neuromodulation: FDA approved a vagal blocking therapy device (VBLOC®) for the treatment of obesity in January 2015.

Other FDA approves medications

Orlistat (Rx: Xenical®; OTC: alli®): It is a peripherally acting pancreatic lipase inhibitor; reduces absorption of ingested fat. Prescription orlistat is the only weight-loss medicine that is approved for children over the age of 12.

Phentermine/Topiramate ER (Qsymia®): It is a combination of appetite-suppressant sympathomimetic amine and anticonvulsant. It is FDA approved in 2012.

Lorcaserin (Belviq®): It is a selective serotonin 2c (5HT-2c) receptor agonist; stimulates 5HT-2c receptors in the appetite center of the brain. It is FDA approved in 2012. In July 2016, the FDA approved Belviq XR, a once daily form of Belviq.
Both Qsymia and Belviq are C-IV controlled substances. Neither drug is approved for use in children.

Naltrexone SR/Bupropion SR (Contrave®): Bupropion (a dopamine and norepinephrine reuptake inhibitor used to treat depression and smoking cessation) and naltrexone (an opioid receptor antagonist used to treat addiction). Effects may occur in the hypothalamic appetite center or the mesocorticolimbic dopamine system and other brain areas related to reward-driven behaviors. FDA approved in 9/2014.
In clinical trials, 36-48% of patients lost at least 5% of body weight compared to placebo.

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ANESTHESIOLOGY 2017
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Top 10 Respiratory Anesthesia Practices That Drive Me Crazy

David O. Warner, M.D. **Rochester, MN**

As ever-more sophisticated ventilators are incorporated into anesthesia machines, there is increasing confusion regarding both the physiological principles pertinent to perioperative respiratory management and their clinical implications. Many of the practices commonly employed have little or no evidence to support them, nor are they supported by a convincing physiological rationale. This lecture is my opportunity to vent about some of our irrational or sloppy practices, and is designed to be deliberatively provocative. The conclusions may be open to debate, but hopefully any such debate will help you consider your practice on the basis of evidence and physiology, rather than on the basis of "that's how we've always done it". Here are my personal top 10 (in no particular order).

1. Wimpy preoxygenation

Preoxygenation prior to anesthesia induction is a time-honored procedure applied routinely in anesthesia practice. When properly performed, it prolongs the duration that apnea can be maintained without arterial oxygen desaturation, a useful outcome if unanticipated airway difficulties arise. However, proper technique is often not applied. For example, the facemask is lightly placed on the patient's face, such that there is significant entrainment of room air around the edges of the mask. The facemask seal must be sufficient so that all the inspired gas comes from the anesthesia circuit and bag, rather than via room air entrainment. .Because peak airflow during inspiration may approach 60 L/min, with typical fresh gas flows of 6 L/min the effective inspired oxygen fraction is approximately 40% if a proper seal is not obtained. This will significantly reduce the apneic time prior to desaturation. Many ventilatory maneuvers during preoxygenation have been described, ranging from normal tidal breathing to vital capacity inspiration, most of them equally efficacious, but all depend on an adequate mask fit. One way to objectively evaluate the quality of preoxygenation is to monitor the end-tidal oxygen fraction – aim for at least 80% prior to proceeding.

So take the time to do it right, every time – and monitor the efficacy of your technique.

2. "Routine" ventilator settings

Many anesthesiologists were taught in training to use the following ventilator settings intraoperatively: tidal volume = 10 ml/kg and rate = 10-12/min. These settings will routinely produce significant hyperventilation. The rationale for these settings includes:

1) higher tidal volumes will prevent atelectasis and improve oxygenation;

2) respiratory rates of 10-12 are physiologic, and;

3) hypocarbia is good, hypercarbia is bad.

However…..

1) High tidal volumes, at least in the ranges used to maintain ventilation in modern practice, do not prevent or reverse atelectasis and do not consistently improve gas exchange. Resolution of intraoperative atelectasis requires "recruitment maneuvers" (prolonged, high airway pressures), not higher tidal volumes – as we will see in point #5 below. Indeed, higher tidal volumes certainly hurt lungs that are already injured, and may have deleterious effects in

even normal lungs.

2) Because metabolic demands are decreased during anesthesia, it is not necessary to maintain an "awake" respiratory rate…which in any event widely varies among individuals;

3) Other than for some neurosurgical cases, hypocapnia is not beneficial. Indeed, there is some evidence that hypercarbia may be beneficial. For example, hypercarbia causes peripheral vasodilation and increases tissue oxygenation, which could help prevent wound infection (although this remains to be shown). There is also fascinating study (which to my knowledge has not been repeated) suggesting that intraoperative hypocapnia delays emergence.

So consider using lower tidal volumes (in the 5-6 ml/kg range) and lower breathing frequencies that will maintain at least normocarbia.

3. "Routine" use of mechanical ventilation and paralysis

Anesthesiologists in the US frequently employ pharmacologic paralysis and mechanical ventilation, even for cases in which neuromuscular blockade is not required to accomplish the procedure, or cases in which patients could easily maintain spontaneous breathing. Indeed, when patients move after the induction of anesthesia, the first response is often to administer a neuromuscular blocking drug. After all, the surgeons will be happier and won't yell if the patients don't move, I can use less anesthetic drugs which avoids hypotension and hastens emergence, and in fact we always do it that way. And if I just turn on the ventilator, I don't have to worry about whether the patient will be adequately ventilated – it's a "ventilator", right? Plus, succinylcholine is now "persona non grata" at many institutions, committing patients to extended paralysis if nondepolarizing neuromuscular blocking drugs are used to facilitate endotracheal intubation.

Here are a few reasons to reconsider "routine" mechanical ventilation/paralysis:

1) Positive pressure ventilation requires a more-or-less secure airway. Endotracheal intubation is not a benign intervention; if the only indication for an endotracheal tube is to provide mechanical ventilation, consider whether you really need mechanical ventilation. Many use positive pressure ventilation with supraglottic airways such as the LMA, but remember that unless properly seated, the gas may be delivered to locations you do not wish to receive it (e.g., the stomach).

2) When patients move, they are generally telling you "please give me more anesthesia" rather than "please paralyze me". Use of neuromuscular blocking drugs is a risk factor for intraoperative awareness, which is rare (but not unheard of) in a patient who is not paralyzed. There are many other risks associated with neuromuscular blocking drugs, including anaphylactic and anaphylactoid reactions and postoperative respiratory complications associated with incomplete reversal of block.

3) Just like our anesthetic forefathers (and foremothers), you can learn a lot by watching patients breathe. For example, parameters such as end-tidal CO_2 maintained during spontaneous breathing depend on anesthetic depths, such that central respiratory control mechanisms can serve as an excellent integrated neurophysiology monitor for overall anesthetic effects. This can be a useful tool to help administer anesthesia, for example to titrate opioid supplementation at the end of cases to facilitate smooth, painless emergence. There also may be situations in which gas exchange is better maintained if physiologic diaphragmatic contraction is also maintained, as spontaneous breathing can be associated with improved ventilation-perfusion matching during anesthesia.

So use mechanical ventilation/paralysis because it is specifically indicated for a patient, not as a matter of routine….or as a substitute for adequate anesthesia…

4. "Assisted" ventilation

Patients breathing spontaneously under anesthesia often receive "assistance" – a squeeze on the bag every now and then to augment tidal volume, or in today's world one of numerous modes of pressure support, again designed to augment tidal volumes. Patients with supraglottic airway devices routinely receive "assisted" ventilation via this mechanism, which may cause entry of gas into the stomach if a less than perfect seal is achieved. The rationales behind "assisted" ventilation are that increased tidal volumes will improve atelectasis, and that this practice will augment minute ventilation and prevent hypercapnia.

However, there are inconvenient truths that make this reasoning suspect. We have already discussed that increasing tidal volumes, at least to the relatively modest degree used in "assisted" ventilation, does not improve atelectasis or oxygenation. And is it possible to significantly augment minute ventilation during spontaneous breathing under anesthesia, and still maintain spontaneous ventilatory effort? When patients are breathing spontaneously under volatile anesthesia, there is an "apneic threshold" – a value of arterial PCO_2 below which ventilatory effort (i.e., respiratory muscle activity) ceases. This threshold is 4-5 cm below the arterial PCO_2 maintained during spontaneous breathing, largely independent of anesthetic or the depth of anesthesia. So if you want to maintain your patient's respiratory effort, you can only achieve modest decreases in PCO_2 with "assisted" ventilation.

So although "assisted" ventilation may keep your hand (or your anesthesia ventilator) busy and make you feel like you are doing something useful, the reasoning supporting its use is questionable at best.

5. PEEPed out

General anesthesia nearly always causes atelectasis in dependent areas of the lung, which represents a major (but not the only) source of gas exchange abnormalities during anesthesia. When combined with other abnormalities of chest wall mechanics such as obesity, intraoperative hypoxemia may occur. A frequent response is to simply dial in 5-10 cm H_2O of positive end-expiratory pressure (PEEP) – which sometimes seems to help in ICU patients, right? Unfortunately, the isolated application of PEEP is unlikely to reverse intraoperative atelectasis. Rather, "recruitment" maneuvers are required, involving sustained (30-40 seconds), high (approximately 40 cm H_2O) airway pressures. PEEP applied after recruitment maneuvers can help prevent the reformation of atelectasis. Also, a high inspired fraction of O_2 can accelerate the reoccurrence of atelectasis – so keep the F_IO_2 below 80% if possible. Intraoperative atelectasis can also persist into the postoperative period and cause impairment of gas exchange, so it is worth considering recruitment maneuvers prior to extubation at the end of the case.

The "lung protective" strategy of recruitment maneuvers followed by PEEP and reduced tidal volume benefits critically-ill patients with acute lung injury, and it has been suggested that this may be beneficial even in patients with normal lungs undergoing major procedures. The literature is contradictory as to whether benefit is achieved, but there is certainly no evidence of harm.

So intraoperative hypoxemia is often caused by dependent lung atelectasis, which is best treated by recruitment maneuvers followed by PEEP – don't just turn on the PEEP.

6. Mode madness

Newer generations of anesthesia machines are equipped with sophisticated ventilators that provide many of the same features of those ventilators utilized in intensive care units. These are touted by their manufacturers as major advances in anesthesia technology, and it is indeed fun to play with the dials (or rather the touchscreen) for those who are mechanically inclined.

However, keep three things in mind.

1) There is little to no evidence that any mode of intraoperative ventilation has any effect on outcomes, despite multiple attempts to prove benefits of the latest "mode-of-the-month". This has largely been true even in the intensive care unit – all we really know is that high tidal volumes are bad.

2) The multiple modes of ventilation available on modern anesthesia machines provide multiple opportunities for confusion and misuse. Anecdotal experience suggests that many providers do not really understand how the ventilators operate, and this lack of knowledge can have consequences. For example, providers may assume that the patient is breathing spontaneously with a pressure-support mode, and not recognize the absence of spontaneous ventilatory effort. This can make for an interesting extubation experience.

3) In their zeal to optimize the performance of their ventilators, manufacturers have compromised abilities basic to the functioning of the anesthesia machine (in my opinion). For example, allowing pediatric patients to breathe spontaneously with some modern machines results in significant rebreathing of CO_2.

So if you choose to indulge in mode madness, please recognize that it is for your benefit, generally not for the benefit of your patients, and make sure you understand how that fancy ventilator works.

7. Why is my vaporizer broken?

Now that the monitoring of inhaled and exhaled gases is widespread, anesthesia personnel have noted apparent discrepancies between the set volatile anesthetic concentration and the actual inspired anesthetic concentration, sometimes prompting concerns that there is a malfunction of the machine.

However….remember that anesthesia circle systems allow rebreathing of exhaled gas, with the amount of rebreathing dependent on the balance between fresh gas flow into the circuit and minute ventilation. With lower flows, more rebreathing occurs. If this happens say early in induction, the rebreathed gas will be relatively poor in anesthetic, and the inhaled anesthetic concentration will be less than the set anesthetic concentration. The opposite consideration applies during emergence. This phenomenon is as old as the use of volatile agents and circle systems – but only recently have we had the technology to see it routinely!

So remember that if you wish to rapidly change the inspired concentration of a volatile anesthetic (or to wash out agent at the end of the case), you need to use high fresh gas flows – and don't worry, the vaporizer is fine…..

8. What, no pediatric circuit?

For smaller children, we often use anesthesia circuits with small diameters, and smaller anesthesia bags. Do we really need to use smaller circuit equipment for smaller people? When asked why, people often mumble something about dead space….

However….remember that the dead space in a circle system extends only distal to the Y-junction – the diameter of

the tubing leading to and from the Y-junction makes no difference to dead space. There is the concept of "compression volume" that applies during positive pressure ventilation. This represents ventilation that is "lost" due to the increase in pressure that occurs in the limbs of the ventilator circuit. The lower the volume of each limb of the circuit, the lower the "compression volume". However, the magnitude of this effect is trivial – for normal airway pressures used during intraoperative ventilation, only about 2% of the delivered volume is "lost". So this is not much of a reason to use smaller circuit equipment. It is true that with a smaller anesthesia bag, it is easier for the "educated hand" to detect changes in compliance, tidal volume, etc.

So use whatever circuit you wish for your smaller patients – but don't panic if the "pediatric" circuits are not available.

9. Two puffs is enough

When patients develop intraoperative bronchospasm, they are often treated using aerosolized drugs such as albuterol. However, it can be quite challenging to administer aerosols to anesthetized patients via an endotracheal tube. Even under the best of conditions in ambulatory patients, only a minority of the total amount of drug administered by a metered dose inhaler actually reaches the small airways. Even less is delivered when administered via an endotracheal tube, with only 5-10% of an administered dose being delivered to the airways. Thus, simply attaching a metered dose inhaler to the elbow of the breathing circuit and administered two puffs (hopefully at the right portion of the respiratory cycle) is unlikely to produce an adequate therapeutic effect. Suggestions to improve drug delivery include: 1) consider using nebulizers rather than metered dose inhalers if available in a timely fashion; 2) use a spacer device in the inspiratory limb of the circuit, and; 3) increase the number of puffs to account for decreased efficiency of delivery.

Usually two puffs is <u>not</u> enough – so don't be afraid to administer more puffs to obtain the necessary therapeutic effect.

10. Don't stop smoking!

One of the most pernicious and persistent myths in perioperative medicine is that quitting smoking shortly before surgery will actually increase the risk of pulmonary complications, supposedly because of increased cough and sputum production. Multiple studies have now shown that this is absolutely <u>not</u> true – quitting smoking at any time prior to surgery will not increase the rate of any complication, although it is true that it may take several weeks to realize the full benefits of smoking cessation in terms of reducing the risk of pulmonary complications. Anesthesiologists are in a unique position to help their patients quit smoking, and should take every opportunity to help them do so. Surgery serves as a "teachable moment" for smoking cessation, as having major surgery can double the chances that patients can quit successfully. This will improve both immediate perioperative outcomes and long term health. For more information, see www.quitforsurgery.com

So any time is the right time for patients to quit smoking – even shortly before surgery.

In summary…

You may or may not agree with all these points, but hopefully this presentation will help you consider the evidence and the physiology that underlies these and other practices in perioperative respiratory management so that you can make your own rational choices.

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ANESTHESIOLOGY 2017
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Perioperative analgesia and effect on patient outcomes

Spencer S. Liu, M.D. **New York/NY**

Introduction

Provision of high quality perioperative analgesia has become recognized as an important goal. However, ability of analgesia to improve outcomes remains controversial. [1] A key component of this continuing controversy is that individual clinical trials need large patient sample sizes due to the current relatively low incidences of major postoperative morbidity. Thus, this lecture will focus on studies with large subject samples to evaluate effects of postoperative analgesia on major postoperative outcomes. Most discussed evidence involves epidural analgesia, as this is the most studied regional anesthesia/analgesia technique for major postoperative outcomes. Furthermore, the lecture will discuss effects of regional analgesia on patient oriented outcomes. As anesthesia and perioperative care become increasingly safe, these patient oriented outcomes may assume greater importance.

Effect of regional analgesia on major morbidity

Epidural analgesia

Mortality

Meta-analyses: The largest meta-analysis of RCTs was published in 2000 (CORTRA) and included 141 RCTs (through Jan 1, 1997) with 9,559 patients undergoing a variety of surgical procedures [2]. This meta-analysis examined effects of neuraxial block (spinal anesthesia, epidural anesthesia, and epidural analgesia) vs general anesthesia, but results from this meta-analysis likely apply to perioperative epidural analgesia as 66 of the RCTs with 4,498 of the patients utilized epidural anesthesia and analgesia. This meta-analysis observed a reduction in mortality with neuraxial blockade (1.9% vs 2.8%, OR 0.7 with 95% CI 0.54 to 0.9) and specifically for thoracic epidural blocks (1.5% vs 2.9%) and orthopedic procedures. A recent (2014) meta-analysis of only Cochrane systematic reviews did not report an effect on mortality with use of neuraxial anesthesia vs general anesthesia . [3]

Several procedure specific meta-analyses have been conducted, and all report inconclusive effects on mortality with epidural analgesia for open abdominal aortic surgery [4], coronary artery bypass grafting [5], abdominal surgery [6], and hip and knee replacement surgery [7].

Randomized Controlled Trials: The most recent large RCT was conducted in 2011 in 654 patients undergoing cardiac surgery that were randomized to combined general/thoracic vs general anesthesia. [8] This RCT did not note any differences between groups in mortality (0.6 vs 0.3%). 2 large RCTs have been performed in non-cardiac surgery patients. In 2001, the Veterans Affairs Cooperative Studies Program (VACS) randomized 984 patients (all or mostly men) undergoing 4 types of surgery (aortic, gastric, biliary, or colon) to combined general/epidural anesthesia followed by epidural morphine vs general anesthesia followed by systemic opioid treatment [9]. Approximately 85% of the epidurals were placed at the thoracic level. Overall mortality rates were similar between groups (4 vs 3.4%). In 2002, the Multicentre Australian Study of Epidural Anesthesia (MASTER) trial [10] enrolled 915 high risk patients (prospectively defined in the protocol) who had undergone mixed abdominal surgical procedures and were randomized to combined general/epidural anesthesia followed by 72 hours of postoperative epidural analgesia (low thoracic or high lumbar placement) with local anesthetic and opioids vs general anesthesia followed by systemic opioid treatment. This RCT was limited by poor protocol compliance, as only 225/447 patients fully adhered to the epidural analgesia protocol. Overall mortality rates were again similar between groups (5.1 vs 4.3%).

Clinical registries: In 2008, a propensity score analysis of a single institution electronic registry of 259,037 patients undergoing mixed surgery reported a significant reduction in 30 day mortality in patients selected for epidural anesthesia/analgesia (n=56,556) of 1.7% vs 2%. [11] In 2004, a 5% random sample of the Medicare claims database. Patients undergoing a variety of surgical procedures were stratified to the presence (n=12,780 subjects) or absence (n=55,943) of coding for postoperative epidural analgesia. [12] After adjusting for comorbidities, age, gender, and hospital size, regression analysis revealed that the presence of postoperative epidural analgesia was associated with a significantly lower incidence for both 7-day (0.5 vs 0.8%, OR = 0.52 with 95% CI 0.38 to 0.73) and 30-day (2.1 vs 2.5%, OR = 0.74 with 95% CI 0.63 to 0.89) mortality [12]. There was a significantly lower mortality in patients who received postoperative epidural analgesia for higher-risk procedures (e.g., lung resection, colectomy) but not lower-risk procedures (e.g., total knee replacement, hysterectomy) or in patients with lower comorbidity indices. Although

the number of patients from these registry analyses is impressive, these data are limited by retrospective nature, accuracy of coding for complications, and degree of association between epidural analgesia and outcomes.

Summary statement: There is modest evidence for reduction of mortality with epidural analgesia for non-cardiac procedures. The largest meta-analysis observed a reduction with neuraxial block. Procedure specific meta-analyses and individual RCTs have not noted an effect from epidural analgesia but lack sufficient sample size due to the relatively low incidence of mortality (0.2-5%). Analysis of clinical registries offers large patient numbers and a modest association between epidural analgesia and reduced mortality.

Cardiovascular

Perioperative cardiac complications remain common, and recent evidence suggests that even subclinical myocardial injury (e.g., TnT of 0.03 ng/ml) is associated with a 4 fold greater risk of death[13]. Uncontrolled postoperative pain may contribute to cardiac morbidity through activation of the sympathetic nervous system, surgical stress response and coagulation cascade. Experimental data suggest that thoracic epidural anesthesia with local anesthetics can reduce sympathetic activation and provide a favorable balance of myocardial oxygen, but lumbar epidural anesthesia may not provide the same physiologic benefits as thoracic epidural anesthesia [14,15].

Meta-analyses: Six meta-analyses were identified that examined efficacy of epidural analgesia on cardiovascular events [2,3,16-18]. The largest was the previously described CORTRA meta-analysis that reported a non-significant decrease in the risk of myocardial infarction (0.9% vs 1.3%). It should be noted that the majority of patients received lumbar epidural or spinal anesthesia, which may not provide the physiologic benefit of TEA.

Three smaller but more specific meta-analyses examining the efficacy of postoperative epidural analgesia and cardiovascular events suggest a benefit for epidural analgesia and TEA in particular for open major vascular procedures. The meta-analysis by Popping in 2008 in abdominal and thoracic procedures noted a significant reduction in myocardial infarction with primarily thoracic epidural analgesia (2.6 vs 4.6%). Beattie et al noted a significantly lower incidence of myocardial infarction in those who received epidural analgesia (rate difference = -3.8% with 95% confidence interval of -7.4% to -0.2%; p = 0.049) primarily in vascular surgery patients (579 out of 632 patients), and analgesic subgroup analysis revealed that TEA but not LEA provided a significant reduction in the rate of myocardial infarction (3.6% vs 8.5%, rate difference = -5.3% with 95% CI of -9.9% to -0.7%). A similar but more procedure specific meta-analysis of open abdominal aortic surgery with 1,224 patients (through June 2004) noted significant reduction in risk of cardiovascular complications (RR 0.74 with 95% CI 0.56-0.97) and myocardial infarction (RR 0.52 with 95% CI 0.29 to 0.93) with epidural vs systemic analgesia [4]. Subgroup analysis again indicated that only TEA and not lumbar epidural analgesia was associated with reduced risk of myocardial infarction. These findings would support the experimental data demonstrating physiologic cardiac benefits of thoracic but not necessarily lumbar epidural analgesia. Another procedure specific meta-analysis examined 28 RCTs with 2731 patients undergoing coronary artery bypass surgery with or without TEA. [5] Myocardial infarction was not reduced with an odds ratio of 0.81, but significant reduction in risk of dysrhythmias was noted with TEA (RR 0.68 with 95% CI 0.5-0.93). Other procedure specific meta-analyses examining effects of epidural analgesia on abdominal, and hip and knee replacement surgery concluded that there was insufficient evidence to analyze cardiovascular complications. [6,7,17]

Randomized Controlled Trials: The large RCT of 654 patients undergoing cardiac surgery did not note any differences between groups in myocardial infarction (4.9% in both groups). [8] The VACS trial did not note a significant reduction in cardiovascular complications (myocardial infarction, heart failure, dysrhythmias, severe hypotension) with use of epidural morphine (8.6 vs 11.2%) for all patients [9]. However, the abdominal aortic surgery subgroup (n=374) had significantly lower incidences of cardiovascular complications (9.8 vs 17.9%, p=0.03) primarily due to reduction in myocardial infarction (2.7 vs 7.9%, p=0.05). The MASTER trial did not note significant differences between groups.

Summary statement: There is consistent evidence that thoracic epidural analgesia may reduce the risk of cardiovascular complications, especially myocardial infarction, in patients undergoing open major vascular surgery and dysrhythmias in patients undergoing cardiac surgery. This is likely due to a higher underlying rate of cardiovascular complications for this surgical population (4-37%).

Pulmonary

Postoperative pulmonary complications (PPCs) are as common as cardiac complications for patients undergoing non-cardiac procedures, and may carry the same risk of increased mortality and length of hospital stay [19]. The pathophysiology of postoperative pulmonary complications (PPC) after surgery is multifactorial and may include disruption of normal respiratory muscle activity from either surgery or anesthesia, a reflex inhibition of phrenic nerve activity with subsequent decrease in diaphragmatic function, and uncontrolled postoperative pain [20]. Epidural analgesia will confer superior analgesia thus improving voluntary pulmonary function [21]. Segmental block from thoracic epidural anesthesia may result in increased tidal volume and vital capacity related in part to improved pain control and also to interruption of the reflex inhibition of phrenic nerve activity, thus improving diaphragmatic activity.

Meta-analysis: In the CORTRA study, neuraxial block in mixed surgical procedures was associated with significantly decreased risk of pneumonia (3.1% vs 6%, OR 0.61 with 95% CI 0.48-0.76) especially with TEA (OR 0.48 with 95% CI 0.35 to 0.67) vs spinal anesthesia or lumbar epidural anesthesia (OR 0.76 with 95% CI 0.55-1.04) [2]. This finding would support the underlying potential physiologic benefit for TEA for reducing PPCs. This finding was confirmed in the 2008 meta-analysis (n=5,904) by Popping et al that noted a significant reduction in pneumonia with primarily thoracic epidural analgesia (8 vs 12%) in patients undergoing abdominal or thoracic surgery. [18] The 2014 systematic review of Cochrane systematic reviews also reported a reduction (OR 0.46) in postoperative pneumonia with use of neuraxial anesthesia. [3]

More procedure specific meta-analyses were also identified. Use of TEA in coronary artery bypass surgery (n=2,731) was associated with significantly decreased risk of PPC (RR 0.53 with 95% CI 0.4 to 0.69). [5] Use of TEA in open abdominal aortic surgery (N= 861) was associated with significantly decreased risk of respiratory failure (RR 0.63 with 95% CI 0.51-0.79) [4].

Randomized Controlled Trials: The large RCT of 654 patients undergoing cardiac surgery did not note any differences between groups in pulmonary complications (9.2 vs 5.8%). [8]The VACS study observed a non-significant reduction in respiratory failure for all patients in the epidural group (9.9% vs 14%) [9]. However, subgroup analysis of the abdominal aortic surgery subgroup (n=374) noted a significant reduction in respiratory failure with use of epidural analgesia (14% vs 28%, p<0.01). The MASTER study (N=915) found observed similar findings with a lower incidence of respiratory failure in the epidural analgesia group for high risk patients undergoing mixed abdominal surgical procedures (23 vs 30%, p=0.02) [10]. As described above, most epidurals were placed at the thoracic level for both RCTs.

Summary statement: There is consistent evidence from meta-analyses and large RCTs that thoracic epidural analgesia reduces risk of postoperative pulmonary complications, especially in high risk surgery.

Gastrointestinal

Postoperative ileus is very common after abdominal surgery (>90% in many series) and may increase resource utilization by prolonging hospital stay [22]. Although the pathophysiology of postoperative ileus is multifactorial, primary mechanisms include neurogenic (spinal, supraspinal adrenergic pathways), inflammatory (i.e., local inflammatory responses initiate neurogenic inhibitory pathways), and pharmacologic (e.g., opioids) mechanisms [23]. Epidural analgesia provides superior pain control and marked sparing of opioid consumption [21]. Sympathetic block from epidural local anesthetics may attenuate postoperative reflex inhibition of GI motility. Suppression of the surgical stress response and systemic absorption of epidural local anesthetics may reduce the inflammatory response to attenuate postoperative ileus [22,23]. Consistent with these mechanisms, experimental data consistently indicate that epidural analgesia with local anesthetics shortens time of intestinal paralysis, increases the strength of colonic contractions, and does not impair anastomotic healing or increase risk of anastomotic leakage [24].

Meta-analysis: A Cochrane Library meta-analysis that included 22 RCTs with 1,023 patients undergoing abdominal surgery [25] and a meta-analysis from 2007 (n=806) both noted consistent reduction in postoperative ileus with epidural analgesia with local anesthetics.

Summary statement: There is consistent evidence from meta-analysis that epidural analgesia with local anesthetics hastens return of postoperative GI function after abdominal surgery by 24 to 37 hours.

Cancer recurrence

The immune system is critical for ability to detect and eliminate cancer cells. Current evidence suggests a primary role for NK cells for "elimination, equilibrium, escape" process. The immune system is initially able to eliminate cancer cells. However, natural selection over time results in resistant cancer cells that are contained in an equilibrium state. Disruption to the immune system, such as surgical stress, may tip the equilibrium into an escape phase that allows metastases. Multiple perioperative factors may be involved in the equilibrium/escape phase, and regional anesthesia/analgesia may play a protective role. [26] Laboratory evidence indicates that acute pain suppresses NK cell activity, increase adrenergic activity, and is associated with tumor development in animals. Conversely, relief of postoperative pain reduces postoperative metastasis in rats. Proposed mechanisms for beneficial effects of regional anesthesia/analgesia include attenuation of perioperative immunosuppression, decreased use of volatile and opioid agents, and improved tissue oxygenation. There are currently no prospective large scale RCTs specifically designed to support or refute this theoretical benefit. Most current evidence is either observational or post-hoc re-analysis of a RCT designed for a different hypothesis. Initial data were very favorable for the ability of regional anesthesia/analgesia to reduce risk of cancer metastasis, however subsequent data, including minimally invasive surgery patients, were more equivocal. [27,28]

Summary statement: There is a lack of evidence from well designed prospective studies to support or refute a role for regional anesthesia/analgesia and cancer recurrence.

Effect of regional analgesic technique on patient oriented outcomes

As risk of major perioperative complications decrease, patient oriented outcomes are increasingly being viewed as valuable. Indeed, patient oriented outcomes such as postoperative pain or nausea are consistently rated as top priorities in patient surveys. Unfortunately, there are few validated tools for measuring patient evaluation of such outcomes, as most tools are uni-dimensional and do not recognize patient preferences for different combinations of outcomes and linked side effects. [29]

Epidural Analgesia

Analgesia: Two meta-analyses have compared epidural analgesia to systemic analgesia for mixed surgical procedures.[9,10] For both meta-analyses, epidural analgesia (compared to systemic opioids including intravenous patient-controlled analgesia [IV PCA]) provided statistically superior analgesia at rest and with activity for all types of surgery through postoperative day (POD) 4. Greater improvements were noted when the regimen included local anesthetics and when level of epidural catheter matched site of surgery (e.g., thoracic catheter for thoracic surgery). Multiple procedure specific meta-analyses have also been published[13-16], and all consistently note statistically significantly lower pain scores with epidural techniques.

Side effects: The meta-analyses from 2003 and 2005 also reported on incidences of side effects. As expected epidural and IV PCA analgesia offered different profiles of side effects with epidural analgesia associated with significantly reduced risk of nausea and sedation but significantly higher incidences of pruritus, urinary retention, and motor block. When continuous epidural analgesia was compared to patient controlled epidural analgesia, patient controlled epidural analgesia offered a reduced risk of side effects with significantly lower incidences of nausea and motor block but greater incidence of pruritus.

Summary statement: Epidural analgesia provides superior analgesia to any form of systemic opioid including IV PCA delivery for at least the first 3 POD for a variety of surgical procedures. Use of local anesthetics can maximize this efficacy. Side effect profiles differ between regimens

Continuous peri-neural analgesia

Analgesia and side effects

A meta analysis published in 2006 (19 RCTs with 603 patients) compared continuous peri-neural analgesia vs. mixed systemic opioids (13 of 19 RCTs used IV PCA).[25] Peri-neural analgesia, which can be used on an ambulatory basis[27], provided statistically superior analgesia at rest and with activity for 48-72 hours with a reduction in risk of nausea, sedation, pruritus but increased risk of motor block.

Functional outcomes

Several population based cohort studies and RCTs suggest that use of perineural analgesia can be used to shorten length of stay of major orthopedic procedures such as total shoulder, knee, and hip replacement by nearly 30 %. [30-32] After total shoulder replacement, patients were randomized to saline or ropivacaine via an interscalene catheter. Patients receiving ropivacaine achieved prospectively defined discharge criteria in 21 vs 51 hrs ($p<0.001$). After total knee replacement surgery, 178,214 patients were studied in a cohort design. Thirty five % of patients received a peripheral nerve block and in this group both length of stay and readmissions were significantly reduced. After total hip replacement surgery, patients were randomized to saline or ropivacaine via a lumbasr plexus catheter. Patients receiving ropivacaine achieved prospectively defined discharge criteria in 29 vs 51 hrs ($p<0.001$). Long term investigations have also followed these same patients out for a year after surgery to determine if early superiority in functional outcomes with regional analgesia is preserved. However, no differences in health related quality of life were noted between groups. [33] A RCT randomizing patients to TEA/GA vs GA for off-pump CABG noted that TEA resulted in better analgesia, less sedation, faster time to tracheal extubation, and shorter length of ICU and hospital stay. [34]

Ambulatory surgery now comprises 60-70% of surgical volume. Regional analgesia also appears to have similar salutatory effects for ambulatory surgery. Patients undergoing shoulder or foot/ankle ambulatory surgery were randomized to receive either patient controlled regional analgesia with ropivacaine (via interscalene or popliteal catheter) versus patient controlled intravenous analgesia with morphine. Patients receiving regional analgesia had statistically superior pain control, less side effects, and greater degrees of independent activity for the first 3 days after surgery. [35] Indeed, recent case series suggest that use of perineural analgesia can convert total shoulder, hip, and knee replacement from fully hospitalized to ambulatory surgery stays. [36,37]

Finally, a recent narrative review noted that use of peripheral regional anesthesia was strongly associated with reduction in pain scores and/or opioid use and improved patient satisfaction. [38]

Summary statement: Meta analysis indicates that continuous peri-neural analgesia provides superior analgesia for up to 48 hours after surgery with reduced side effects when compared to systemic opioids. Recent clinical trials suggest use of perineural analgesia may decrease hospital stay for major orthopedic procedures and improve functional status at home after ambulatory surgery.

Summary and Future Directions

Regional analgesia has modest beneficial effect on mortality. Epidural analgesia reduces cardiopulmonary complications in major open procedures such as open aortic repair. Epidural analgesia with local anesthetic containing solutions consistently reduces duration of ileus after open abdominal procedures. Beneficial effects have been reduced by current low rates of postoperative complications and increased use of minimally invasive surgery such as laparoscopic colectomy. [39] Effects of regional anesthesia/analgesia on cancer recurrence are of great interest but await high quality prospective data. Patient oriented outcomes have become an increasingly important field for investigation. Epidural analgesia consistently provides superior analgesia to systemic opioids and a different package of side effects. Perineural analgesia consistently provides superior analgesia and reduced side effects compared to systemic analgesia and may reduce length of stay after major orthopedic procedures.

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ANESTHESIOLOGY 2017
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The Qualities of Leadership and the Ability to Inspire

Samuel Wald, MD, MBA **Stanford, CA**

INTRODUCTION

Many of us operate under the belief that success in leadership involves an innate skill. However, the qualities and behaviors of great leaders can be learned, practiced and refined. Additionally, there is no one best style of leadership as everyone has a different set of strengths and weakness that relate to their abilities as a leader. Independent of our specific job description or role, we are all leading others in some respect as a member of a team. Even though anesthesiology is the practice of an individual, we are in almost all circumstances a part of a team as an inherent part of our jobs. Additionally, our specialty lends itself to enormous leadership opportunities in health care at the departmental, hospital and national levels.

TRAITS OF SUCCESSUL CEOS

One place to look for leadership qualities that produce successful and some unsuccessful outcomes would be to analyze the inner workings of Chief Operating Officers. Certainly, by definition, these individuals would exemplify leadership in practice. A recent article analyzed and described the successful traits of CEOs and found that Decision-making, Engagement, Adaptation and Reliability were all determinates of success as a leader. Anesthesiologists have traits that are aligned with many of these qualities and can be developed further for an impact outside the operating room.

The first striking revelation was making decisions in a timely manner with conviction was more important than making the exact right decision. The context is important, as in clinical practice, we must make rapid decisions and they must be correct with consequences of poor patient outcomes for a hasty decision. The key here is that with ambiguity, the top CEOS are about to make decisions with conviction and are comfortable in unfamiliar domains. This type of process is in contrast to our training as physicians as we seek very targeted decision-making processes and strive for familiarity and consistency in our environment. One concept that might also be difficult to grapple with as a physician is that as a leader an incorrect decision may be better than no decision at all. Our propensity for intellectual complexity may cause a struggle with decisiveness. Slow decisions from a leader can produce bottlenecks and teams may become frustrated or model a cautious approach which can limit the ability of the organization to act. As an anesthesiologist, we often can relate to the premise that we may not always have perfect information and so we analyze the risks and benefits and move forward. This is aligned with the early decision making with conviction as a leader outside the operating room.

Engagement starts with gaining insight the priorities of others and working on the delivery of good outcomes. Doing so with calmness under pressure is also important and within the skill set of anesthesiologists. One needs not necessarily try to be liked by everyone, but respect for stakeholder interests and instilling confidence will lead to high-performance as an engaged leader. Sometimes this requires making uncomfortable decisions that are unpopular and negotiating conflicting viewpoints, but in a respectful manner helps engagement. Engaged leaders engage in conflict, but in the most respectful manner allowing all points of view to be expressed, but not necessarily driven by consensus for a final decision.

Another area where our skills as anesthesiologists are particularly suited is for proactive adaptation. Comfort with facing new situations that require creativity and adjustment to changing conditions is a critical skill. One part of this that would be a different challenge to our roles as anesthesiologists is to spend the majority of our time considering the long-term goals and strategies. Our planning in the operating room usually involves short periods on time from seconds to minutes to hours. Even those in management positions usually deal with days and weeks for OR scheduling, not timelines of months and years. Looking at a longer timeline allows for the recognition of early signs rather than a reactive set of behaviors. It is also important to recognize mistakes and use them as part of adaptation

to learn how to deal with them. Much as we analyze a patient complication and try to learn from it, our focus on improving patient safety can be applied as part of a strategy in the development of leadership qualities.

Of all the four essential traits of CEOs the most powerful is he ability to reliably produce results. Predictability and reliability build trust in our teams and our stakeholders. We know this to be true in our operating room environment and those of us who set reasonable expectations and deliver on them are successful. The skills in predictably planning and delivering a reliable anesthetic can be applied as a leadership quality in the context of managing a team.

Success in leadership is not a function of permanent and unchangeable qualities.

INPIRATIONAL LEADERSHIP

Inspiring leaders use unique combination of their strengths to motivate individuals and teams to take on bold missions plus hold those individuals accountable for producing results.

Likely one of the most important concepts is that a successfully inspirational leader must be true to themselves. It may be tempting to look at other leaders to imitate, but that will not produce authenticity. Certainly, observing and considering the experiences of others is part of learning leadership, to for the trust of others, your genuine self must be presented. One place to start is with your own life story and a reflection upon your own personal experiences. Through that context you can find a place for inspiration for your impact upon the world.

You have your own set of beliefs and convictions and the first step in discovering them is to see how you hold to them under pressure. When things are going well, they may be easy to list and abide by, but in the face of adversity, your values will be tested and this circumstance will expose what is truly most important and what you are willing to sacrifice. Ultimately, your leadership principles are values translated into action determined by your behaviors. One exercise would be to observe yourself under conditions of stress and see which principles you use for leading. Ask for feedback from others. As a corollary, you cannot be an inspirational leader alone. Empowering others on your team and leaders at all levels of the organization will be inspired by your actions and then inspire those around them.

One needs only one strong attribute of inspiration to be successful in this domain. The right inspirational leader for motivation is contextual to the needs of the organization and that are right for motivating leader's specific strengths. There are is one universal set of qualities for inspirational leaders which includes remaining calm under stress, empathizing, listening, and remaining present.

To help gain these qualities a great deal of attention has been focused recently on emotional intelligence. Travis Bradberry and Jean Greaves have outlined some of the habits of highly emotionally intelligent people which can all be strengthened through insight and practice. They are relentlessly positive and release what they can't control. They have power in attention and effort and a robust emotional vocabulary. Unlabeled emotions will be misunderstood and lead to irrational choices. Emotionally intelligent people make specific word choices and focus on more directed actions. Assertive is important, but balanced with good manners, empathy, and kindness with an ability to assert and establish boundaries. This is ideal for handling conflict. Curiosity about other people will provide empathy and an ability to listen. One can forgive, but without forgetting. However, it is key to forgive to prevent a grudge. Making things fun and finding joy where you are able fights off stress and builds lasting resilience. Be difficult to offend with a firm grasp of whom you are, self-confident and open-minded. This can be facilitated by squashing negative self-talk. One method is to stop pessimistic things by writing them down which will slow down negative momentum to be more rational and clear.

CHARISMA

One does not have to be charismatic in order to be an inspirational leader, but for those of you who inspire to refine your own charismatic traits there are some tips to consider:

1. You don't have to be the most attractive person in the room.
2. Always be present.
3. Be an excellent listener by pausing and asking questions deliberately.
4. Don't compare yourself to others.
5. Combine your power with warmth to create a full, charismatic package.

Just as there is no one form of inspirational leadership and one must remain authentic, there is also no one charismatic style.

Charismatic Styles:

Focus: People to feel like they're the only ones in the room with you.
Visionary: This style makes other people feel inspired.
Kindness: Based mostly on warmth and body language
Authority: Powerful charisma style, but not likeable all the time.

No matter what you choose as your style indicators that you can consider are the use of body language, a choice in your appearance, your title and reflection of the reactions of others.

In her commencement speech at the Stanford University School of Business Mary Barra, the CEO of General Motors summarized what every business school graduate should know and shared leadership lessons she's learned along the way. "Leaders Listen, Leaders Care, Leaders Inspire, Leaders Work."

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ANESTHESIOLOGY 2017
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The Wave of the future: Rescue Transthoracic Echocardiography for Non-Cardiac Anesthesiologists

Learning Objectives:

1) Identify and interpret basic TTE views to assess volume status, ventricular function and basic valvular function
2) Interpret basic lung imaging to assist in diagnosis of pneumothorax and/or pulmonary edema
3) Describe common focused ultrasound protocols (FATE and FEEL) which are utilized for rapid hemodynamic evaluation in the perioperative period
4) Describe the advantage of TTE in clinical assessment and rapid evaluation of issues that are not easily detected by physical examination alone
5) List preoperative co-morbidities which affect patient outcome and that are easily assessed by focused TTE and discuss the use of preoperative TTE to improve decision making regarding postoperative disposition

Josh Zimmerman, MD, FASE **University of Utah**

Presentation 1 – Give me the Basics : Transthoracic echocardiography image acquisition and interpretation

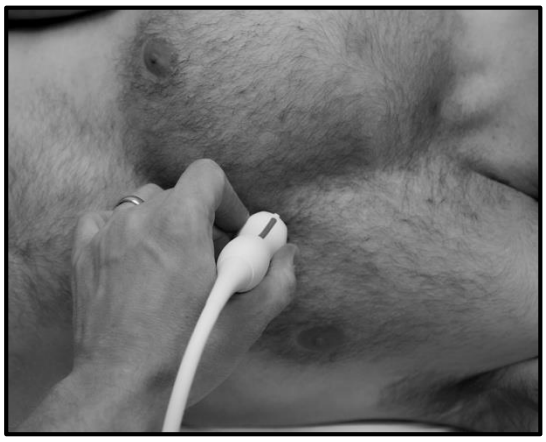
Introduction

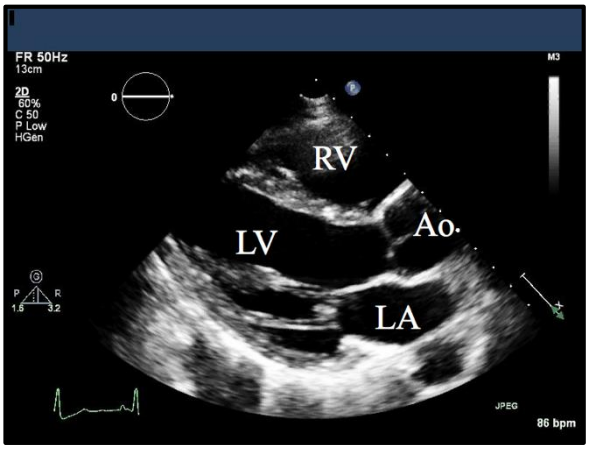
This lecture will cover the basics of bedside transthoracic echocardiography for the assessment of the unstable patient by the non-cardiac anesthesiologist. This is a complex topic and one that obviously cannot be mastered during a single lecture, however the new bedside sonographer will be given a basic introduction as a starting point. During our discussion the techniques required to obtain the basic two-dimensional images will be described, the anatomy of each view will be discussed, and the findings that are likely to be identified in the unstable patient will be described. For readers interested in a more detailed discussion, this topic has recently been reviewed.[1]

Basic Views – Image Creation, Anatomy, and Assessment

Parasternal Long Axis

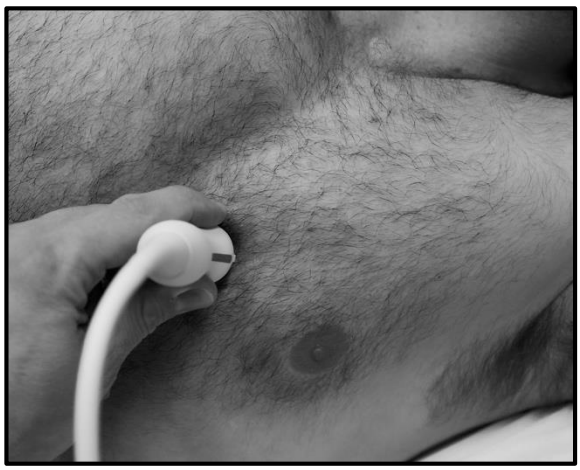
The parasternal long axis view is made with the ultrasound probe placed just to the left of the sternum generally in the 3rd to 5th intercostal space with the indicator pointing toward the patient's right shoulder. The view shows a portion of the right ventricle (RV), the aortic valve, proximal ascending aorta (Ao), left atrium (LA), mitral valve (MV), and left ventricle (LV.) This view should be assessed for chamber size, global left ventricular systolic function, and function of the aortic and mitral valves.

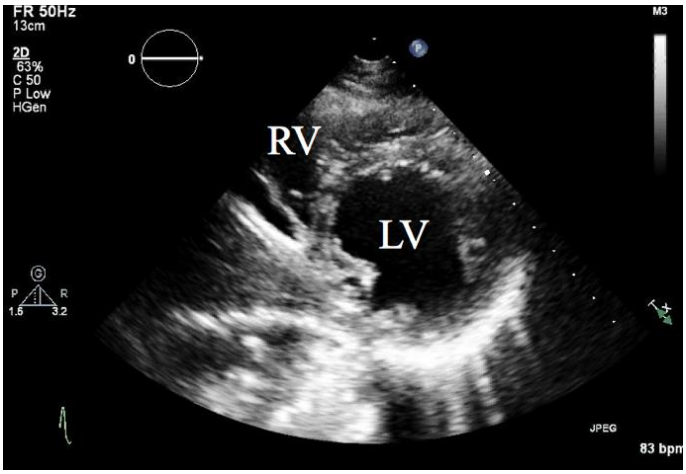




Parasternal Left Ventricular Midpapillary Short Axis

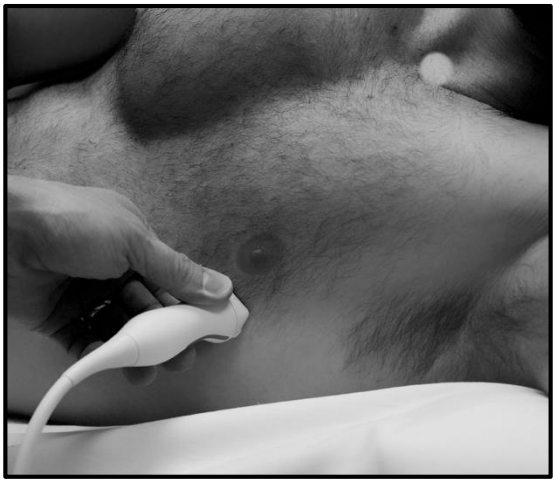
The parasternal short axis view is created by rotating 90 degrees from the long axis, with the indicator pointing toward the patient's left shoulder. This view shows the mid portion of the left and right ventricles at the level of the papillary muscles. It shows 6 segments of the left ventricle representing all 3 coronary distributions. This view should be assessed for global and regional left ventricular systolic function and left ventricular filling.

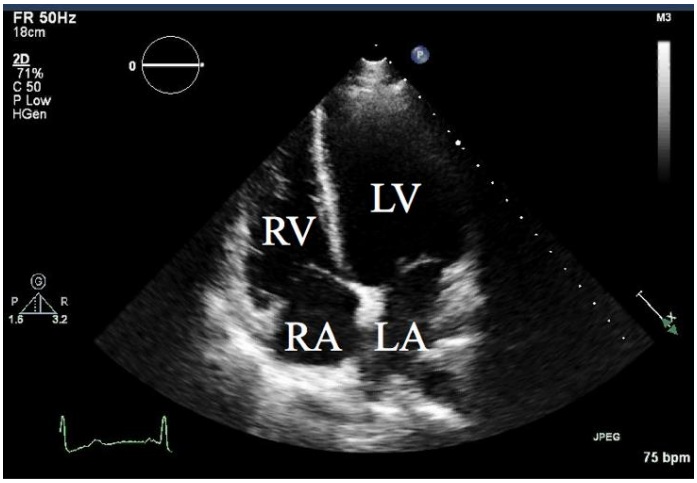




Apical Four Chamber

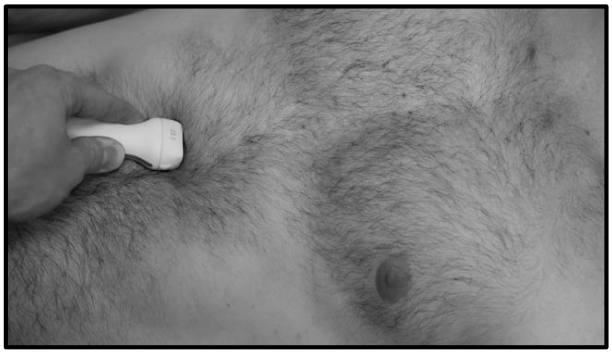
The apical four chamber view is created by moving the probe the LV apex, which can be identified by palpating the point of maximal impulse (PMI.) The indicator will point toward approximately 5 o'clock when viewed from above. This view shows the left and right ventricles, the mitral and tricuspid valves, and the left and right atrium. This view should be assessed for left and right ventricular systolic function and filling, chamber size, and mitral and tricuspid valve function.

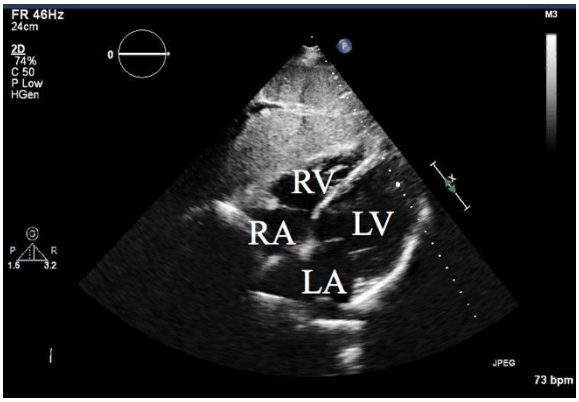




Subcostal Four Chamber

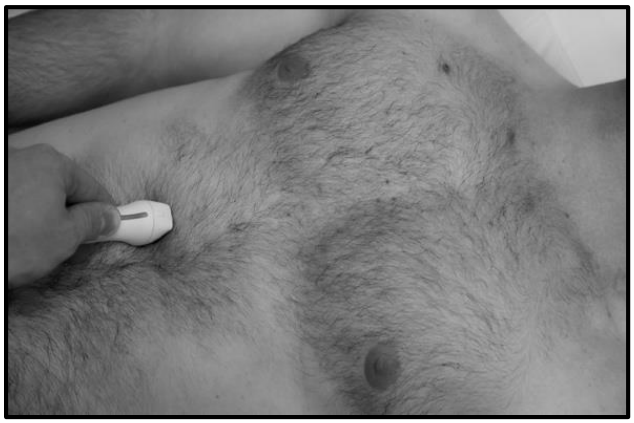
The subcostal four chamber is made by placing the probe below the xiphoid process or slightly toward the patients right, nearly perpendicular to the skin, angled slightly down and toward the patient's left. This view shows the left and right ventricles, the mitral and tricuspid valve, and the left and right atria. This view should be assessed for left and right ventricular systolic function as well as for the presence and significance of pericardial effusion.

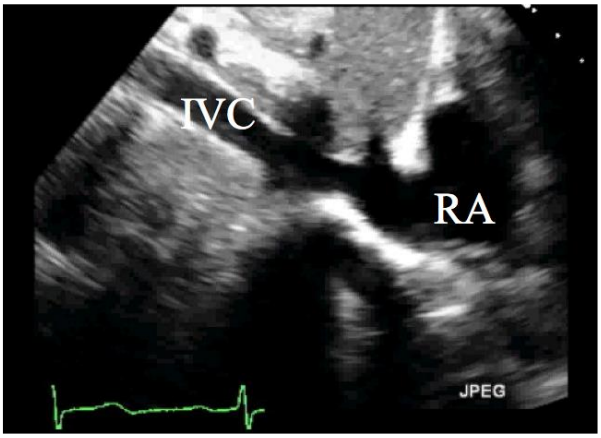




Subcostal Inferior Vena Cava (IVC) Long Axis

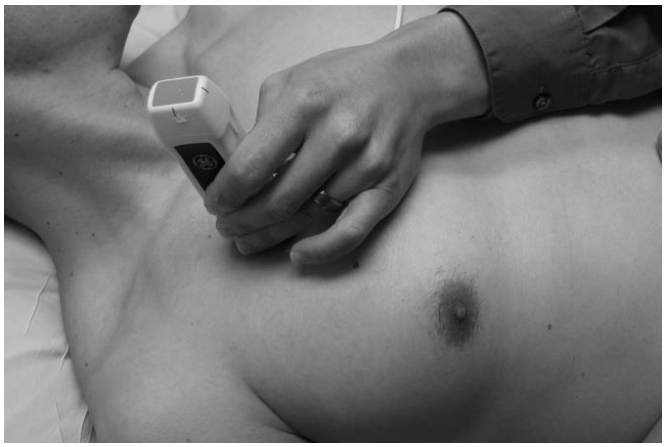
The subcostal IVC long axis is created from the four chamber view by keeping the right atrium in view and slowly rotating the probe clockwise until the IVC is seen entering the right atrium. This view shows the size and behavior of the IVC with ventilation which gives information about right atrial pressure and volume status.

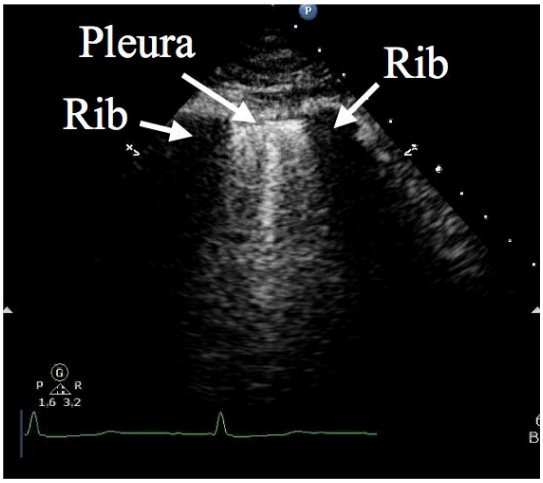




Lung Windows

Each lung should be imaged in at least 6 locations, both superior and inferior locations in the midclavicular line, the midaxillary line, and as far posterior as the patient's position will allow. The probe should placed perpendicular to the skin, with the indicator pointing cephalad. The non-dependent lung fields should be assessed for lung sliding (the presence of which excludes significant pneumothorax), the posterior lung fields should be assessed for evidence of significant effusion, and all lung fields should be assessed for the presence of 3 or more B-lines (lung rockets, comet-tail artifacts) which suggest increased lung water.





Reference:
Zimmerman JM, Coker BJ. The Nuts and Bolts of Performing Focused Cardiovascular Ultrasound (FoCUS). *Anesth Analg*. 2017;124(3):753-760.

Presentation 2 - Now How do I use it? : Preoperative Risk Stratification for Urgent and/or Emergent Surgery
Yuriy Bronshteyn **Duke University**

Cases – Cases - Cases

Moderator
Mary Beth Brady, MD FASE **Johns Hopkins University**

ANESTHESIOLOGY 2017
BOSTON OCTOBER 21-25

Local Anesthetics in 2017: Mechanisms, Toxicities and Controversies From a Clinical Perspective

John F. Butterworth, IV, M.D. **Richmond, Virginia**

General Considerations

Local anesthetics (LAs) and regional anesthesia were introduced to western medicine in 1884 when Köller and Gartner reported topical cocaine anesthesia of the corneas of a frog, rabbit, dog and of each other and when Halsted reported brachial plexus and mandibular nerve blocks in patients.[1] Notable subsequent advances in LAs and regional anesthesia have included: better understanding of LA mechanisms; safer LAs; LAs compounded with novel drugs, microspheres, liposomes, toxins, or other LAs; better needles and infusion devices; more reliable techniques for nerve localization and LA injection; safer techniques for conscious sedation; and more effective resuscitation techniques for LA systemic toxicity (LAST). This review will review the current state of knowledge while focusing on the scientific and clinical implications of studies performed in the past few years.

LA Structures and Chirality

LAs share many structural features. All LAs save for articaine, an agent used almost exclusively in dentistry, have a substituted benzene ring at one end of the molecule and a tertiary amine nitrogen at the opposite end (Figure 1).[2-5] Articaine has as a thiophene (sulfur containing) ring in the place of the benzene ring. LAs are designated either as an ester or an amide based on a chemical linkage in the middle portion of the molecule. Assymetrically substituted (chiral) carbon atoms in compounds that are commercially available as single S(-) enantiomers are designated with an asterix (*) on Figure 1. Mepivacaine has a chiral carbon atom but no asterix because it is only supplied as a racemic mixture. Bupivacaine is either a racemic mixture or a single enantiomer (levobupivacaine) as indicated on the figure. Other compounds that produce local or regional anesthesia have widely varying structures and include: general anesthetics, α_2 agonists, tricyclic antidepressants, alcohols, nerve toxins, cannabinoids, and even 2-heptanone, a honey bee secretion![2,7-15] Perhaps one of these novel compounds will prove safer or more effective than traditional LAs.[16] Indeed there has been extensive work using toxins to enhance the duration and safety of nerve blocks. Preclinical studies have shown prolonged nerve block can be achieved using chemical permeation enhancers, tetrodotoxin (TTX), and epinephrine.[17]

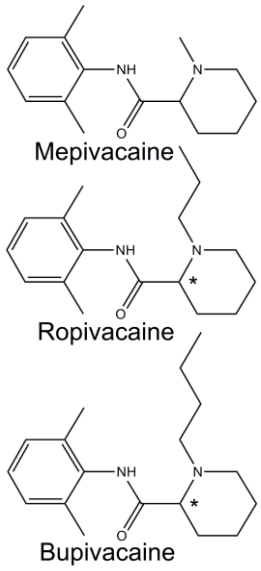


Figure 1

Voltage-gated Na (Na_v) Channels

A sufficient number of Na_v channels must activate and "open" both to initiate Na currents and to propagate action potentials in an axon.[3-5] After being applied on or near a peripheral nerve LAs may migrate into the axonal plasma membranes, where they bind Na_v channels and prevent them from "opening." Similar to the voltage-gated Ca channels from which they evolved, Na_v channels are large, integral membrane proteins containing 1 larger α-subunit and 1 or 2 smaller β-subunits. The α-subunit, the site of ion conduction and drug binding, includes roughly 2000 amino acids and 4 "domains," each with 6 α-helical, membrane-spanning segments. β-subunits regulate activities including channel insertion into the plasma membrane and the voltage-dependence and kinetics of α-subunit gating.[3-5,18]

Humans have 7 genes that code for neuronal Na_v channel α-subunits, 1 gene that code for Na_v α-subunit isoforms in skeletal and and another gene for cardiac muscle, and 1 "silent" nonfunctional Na_v channel α-subunit gene.[18,19,20] Specific Na_v isoforms (gene products) predominate on unmyelinated axons, nodes of Ranvier, and small dorsal root ganglion nociceptors. Genetic variants of Na_v 1.5 (the isoform found only in cardiac muscle) require differing therapeutic drug concentrations.[21] Similarly, Na_v isoforms may have differing drug affinities.[19] Alternative splicing of gene products can yield additional variation, as was demonstrated for Na_v 1.7 channels in human dorsal root ganglia (DRG).[22] Some isoforms may be particularly important in the pathophysiology of chronic pain syndromes or in small-fiber neuropathy.[23] Na_v 1.7 accumulates in painful human neuromas.[23] Na_v 1.8 increases in DRG in animal models of

inflammatory pain and increases in peripheral afferent nerves when there is persisting pain after a spinal cord injury.[24] Increased prevalence of Na_v 1.9 associates with painful diabetic neuropathy. Na_v 1.3 expression in DRG increases after peripheral nerve injury and in human neuromas formed after injury. Na_v 1.6 may underlie repetitive firing in lumbar DRG neurons with inflammation and knockdown of this channel eliminates abnormal spontaneous DRG electrical activity and pain behavior in animals.[25]

Na_v channels exist in at least 3 functional states *in vivo*: "resting," "open," and "inactivated," as was first described by Hodgkin and Huxley.[2-4] During action potentials Na_v channels "open" briefly, allowing Na ions to flow into the cell, depolarizing the plasma membrane. After a few milliseconds, Na_v channels "inactivate" and Na flux ceases. Mammalian myelinated fibers require no contribution from K currents for membrane repolarization, as Na_v channels return to the "resting" conformation with repolarization.[2-4] "Voltage gating" of channel states likely results from small movements of paddle-shaped, voltage-sensing amino acid sequences.[26] Patients with genetic Na_v variants in which "resurgent" Na currents appear during repolarization, presumably from impaired inactivation, may present with a paroxysmal extreme pain disorder (Na_v 1.7), paramyotonia congenital (Na_v 1.4), and long-QT3/sudden infant death (Na_v 1.5), depending on which isoform is abnormal.[20]

Mechanisms of Local Anesthesia by "Classical" and Quaternary LAs

In 1959 Taylor demonstrated that LAs inhibit Na currents yet standard anesthesia textbooks continued to discuss other discredited mechanisms of LA action for more than 30 years! Our knowledge of LA electropharmacolgy is now much more refined. LA binding has been associated with specific regions of the Na_v α-subunit.[3] Some Na_v isoforms are less sensitive to LA or TTX than others.[13,27] LA inhibition of Na currents increases with repetitive depolarizations, often called "use-dependent" block, a phenomenon believed to underlie antiarrhythmic actions of LAs.[2] What is the mechanism of "use-dependent" block? One possibility: repetitive depolarizations increase the fraction of Na_v channels that are "open" or "inactivated" relative to "resting" channels with less LA affinity.[2,19] Alternatively, LAs may preferentially modulate Na_v channel movements associated with opening events.

For many years it has been recognized that humans are very poor models for drug behavior in rats.[28]This has recently been confirmed in a comparison of Na currents in human and rat dorsal root ganglia. Interestingly, there was markedly less use dependent block from lidocaine in certain Na currents from human than from rat ganglia![29]

Compare lidocaine with its quaternary derivative QX-314 in Figure 2. Note QX-314's positively-charged nitrogen (see the "+") as a consequence of QX-314's extra ethyl moiety. When QX-314 is applied *intra*cellularly, this relatively membrane-impermeant agent powerfully inhibits Na currents.[4,5] But does this have relevance to clinical use of LAs where there is no opportunity to deliver agents intracellularly? Recent studies strongly suggest that QX-314 and other drugs may gain entrance to the cytoplasm through vanilloid TRPV1 channels when these channels are activated by pain, lidocaine or capsaicin.[30-32] TRPV1 channel activation underlies nociception in primary sensory afferent fibers.[33] After a greater delay of onset than with lidocaine, quaternary local anesthetics produce prolonged analgesia (perhaps by transit through TRPV1 channels).[34] Recently, infused QX-314 has been shown to relieve cancer induced bone pain in animals by selective inhibition of TRPV1 channels in primary afferent neurons.[35]QX-OH, a new QX-314 derivative, produces analgesia that persists 40-60% longer than QX-314 in animal models, and may be the quaternary LA of choice going forward.[36]

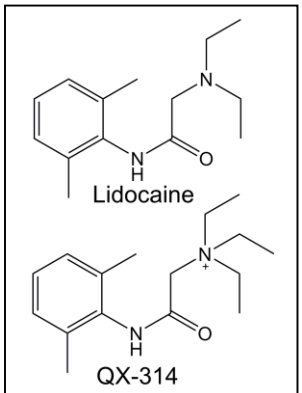


Figure 2

LA Actions at Sites Unrelated to Na_v Channels or Nerve Block

LAs have limited potency and are relatively nonselective. LAs solubilize and disrupt membranes. LAs bind and inhibit channels (including K_{ATP}, Ca release, voltage-gated K, Ca, and HERG), enzymes (including mitogen activated kinases, adenylyl cyclase, and phosphorylases), receptors (nicotinic acetylcholine, NMDA, β-adrenergic, TRPV1, bradykinin B2, 5-HT3), and signaling mechanisms (G-protein-mediated signaling).[2,37] LA binding to these sites could contribute to spinal or epidural anesthesia, useful or toxic effects of systemically absorbed LAs, or (despite being described in myriad publications) have no importance whatsoever![37] Circulating LAs have effects on coagulation, inflammation, microcirculation; immune responses to infection and malignancy, postoperative gastrointestinal function, and analgesia. Infused LAs relieve neuropathic pain and improve perioperative analgesia.[38]

How does iv lidocaine "work?" Does infused lidocaine actually "deepen" general anesthesia? When anesthesiologists were blinded both to intraoperative BIS measurements and to whether IV lidocaine was infused, they gave patients receiving lidocaine reduced concentrations of volatile anesthetics and this resulted in higher BIS measurements! Thus, either BIS may not reflect lidocaine hypnosis or lidocaine does not "deepen" general anesthesia.[39] Infused LAs shorten hospital lengths of stay. Lidocaine inhibits cardiac ischemia and reperfusion injury

in mice by an antiapoptotic effect.[40] Conversely, LAs promote apoptosis and may promote chondrolysis after prolonged intraarticular infusion.[41] Lidocaine and bupivacaine may be worse in this regard than mepivacaine or ropivacaine. LAs inhibit kinesis theoretically inhibiting cancer metastasis. Should we conclude that LAs are the new wonder drugs? Probably not! Other studies suggest that any beneficial effect of LAs or regional anesthesia on cancer progression likely is the result of reduced opioid consumption and not from a direct effect of the LA on cancer cells.[42] Finally, a recent study confirmed that reduced opioid requirements after intraperitoneal LA were the results of local, not systemic, LA actions.[43]

LA Pharmacodynamics

LA Volumes and Concentrations during Nerve Block

During clinical regional blocks, only a vanishingly small fraction of the injected LA molecules will be bound by neuronal Na_v channels specifically or even by neurons generally.[44] Most drug molecules will be bound by other tissues and/or be removed by the blood stream. As noted earlier, clinical regional anesthesia will not arise unless conduction is blocked over a sufficient length of nerve. This "critical length" exceeds 2 cm (far longer than the 3 Ranvier nodes specified in textbooks) except at very increased LA concentrations.[45] Extent and duration of LA effects can be loosely correlated with LA content of nerves in animal experiments.[44,46-48] There is debate as to whether injectate volume, injectate concentration, or mass (volume x concentration) of drug is paramount in determining the success of blocks. In rat sciatic nerve blocks, lower volumes of more concentrated lidocaine produce shorter latencies and longer durations.[48] Nevertheless, human studies often conclude that anesthesia quality improves with increasing mass of drug, whether achieved by increasing volume or concentration.[49.50]

Maximum doses

It is foolish to speak of one, universal, "safe" maximal dose of a LA compound, yet lecturers, textbooks and regulatory agencies perpetuate this nonsense.[51] The maximal tolerable dose depends on many factors, including the site, rate, and duration of LA administration, additives, patient weight and body habitus, and the presence of pregnancy or disease. A LA dose given for intercostal blocks produces greater peak LA concentrations than if given for plexus or epidural blocks.[3,52] A LA concentration in blood produced by a sudden, accidental bolus iv injection may produce CNS toxicity; the same concentration approached gradually over time as a consequence of LA absorption during a perineural infusion may have no discernible adverse effects. Despite the use of ultrasound during nerve blocks complete with direct visualization of nerves and reduced LA doses, accidental intravenous injection and LA systemic toxicity remain a risk.[53]

LA Potency and Duration

Nerve-blocking potency of LAs increases with increasing molecular weight and increasing lipid solubility.[52,54,55] Larger, more lipid-soluble LAs bind Na_v channels with greater affinity and are less readily "washed out" from nerves than smaller, less lipid-soluble LAs. Increased lipid solubility also associates with increased protein binding, longer duration of action, and an increased potency at CV toxicity. Think of the profound reduction in potency, onset delay, and duration of block that result from a methyl for butyl substitution (compare mepivacaine to bupivacaine in Figure 1, with mepivacaine being the smaller, less potent, less lipid soluble agent).

LA Speed of Onset

Generally, the onset of clinical regional anesthesia slows with increasing LA lipid solubility (compare mepivacaine to bupivacaine or chloroprocaine to tetracaine). Curiously, many textbooks describe pKa as inversely related to delay of onset despite contradictory data![52] Chloroprocaine, the agent with the largest pKa, has the shortest delay of onset of all.[56]

Differential Sensory Nerve Block

A LA nerve block that is sufficient to block incisional pain will impair motor function.[2] Smaller fibers can be blocked at lower concentrations of LA than larger fibers of the same type.[2] But, greater LA concentrations are required to block impulses in C fibers than in Aδ or Aβ fibers.[46,57] Bupivacaine and ropivacaine are relatively selective for sensory fibers.[58] As previously noted, differing Na_v channel forms have distinct affinities for LAs and other compounds, and specific Na_v channel gene products are found in unmyelinated nerves, motor nerves, and dorsal root ganglia, offering the tantalizing, as yet unrealized, possibility of selective drugs.[26,59,60]

Other Factors Influencing LA Activity

Many factors influence the quality of local and regional anesthesia, including the dose, site of administration, temperature, pregnancy, diabetes, and additives. In general, the fastest onset and shortest duration of anesthesia occur with intrathecal or subcutaneous injections; a slower onset and longer duration are obtained with plexus and peripheral nerve blocks.[2,52] Pain on injection of warmed LA solutions is less than with room temperature solutions, which hurt less than cold solutions.[61] Pregnancy increases both spread of neuraxial anesthesia and neuronal susceptibility to LAs.[62,63] Diabetic patients and diabetic animals appear to have delayed recovery from peripheral nerve blocks. It is

unclear that this results from increased susceptibility to LAs of diabetic nerves because there is no obvious effect of diabetes upon onset of anesthesia.[64]

Is There Convincing Evidence for Preemptive or Persisting Effects of Local Anesthetics?

Many studies show the need for opioids and other analgesics is greatly reduced following peripheral nerve blocks or local anesthetic infusions and this effect persists for multiples of the local anesthetic elimination half-life. It is likely that absorbed local anesthetic may contribute to analgesia following nerve blocks; however, most studies indicate that actual nerve blocks provide better analgesia than local anesthetic infusions. Whether nerve blocks are administered before or after the surgical procedure does not appear to be of major importance for pain control or outcomes.[38]

LA Formulations for Prolonged Analgesia

After a single injection, with or without additives, LA effects generally will not persist longer than 24 hours. This limitation has led investigators to explore ways to prolong LA actions. Continuous (catheter infusion) blocks and wound infusion catheters represent one approach to prolong the clinical effects of LAs. Lidoderm™ patches provide sustained 24-hour release of topical lidocaine for relief of postherpetic neuralgia. Exparel™ a liposomal suspension of bupivacaine has a licensed indication for administration into the surgical site to produce postsurgical analgesia. After bunionectomy or hemorrhoidectomy (the two procedures that were studied prior to regulatory approval), when combined with opioids this agent produced better pain scores than opioids alone. Nevertheless, there was no difference in pain scores after 24 hrs despite Exparel™ patients requesting less opioid dosing than placebo patients. This agent is being studied for some peripheral nerve blocks with mixed success.[64] Should liposomal bupivacaine be a part of the "local infiltration analgesia cocktail" of dilute local anesthetic and ketorolac increasingly popular for analgesia after arthroplasty? Curiously, a recent large clinical trial has shown no benefit to liposomal bupivacaine vs ropivacaine for local injection after total knee arthroplasty.[65]

LA Additives and LA Mixtures

The most popular LA additives in anesthesia practice (epinephrine, clonidine, opioids, $NaHCO_3$, dextrose, and steroids) are variously added to increase the safety, quality, distribution, duration, and speed of onset of anesthesia, and to reduce blood loss.[2,52,66] Clonidine and dexmedetomidine have LA properties and prolong the duration of many nerve blocks primarily by a local (not systemic) mechanism.[11,67] $NaHCO_3$ increases the fraction of LA molecules that are uncharged, increases the apparent LA potency, and speeds the onset of some nerve blocks.[2,68] $NaHCO_3$ is particularly useful in speeding the onset of anesthesia produced by more "acidic" LA formulations, such as those that are prepared with epinephrine by the manufacturers. Bicarbonate also reduces the pain of local infiltration. Opioids are commonly added to spinal or epidural LAs. Recent preclinical studies have explored combinations of LA with nerve toxins and have measured prolonged analgesia relative to the LA alone.[69]

Mixing of LAs has long been popular. In current practice mepivacaine is often mixed with bupivacaine or ropivacaine in the hope of decreasing the onset delay. Data generally indicate that mixtures yield onset delays and durations of analgesia approximating the mean of the component LAs. Toxicity of mixed LAs appears to be additive.

There are persisting misconceptions about epinephrine. One is that LA-epinephrine solutions are unsafe in patients at risk for coronary artery disease. However, in high-risk patients, epinephrine reduces LA concentrations in blood without producing tachycardia, arrhythmias, or myocardial ischemia.[70] Another misconception is that epinephrine cannot be used in any digital nerve blocks. LA solutions containing epinephrine are now widely used by surgeons for digital nerve blocks.[71] There has been one case report of onset of middle finger ischemia 3 hrs postoperatively after injection of local anesthetic with epinephrine. This patient responded to phentolamine injection at the base of the finger.[72]

LA Blood Concentrations, Protein Binding, Metabolism, and Pharmacokinetics

In blood, all LAs are partially protein-bound, primarily to α_1-acid glycoprotein (AAGP) and secondarily to albumin.[52] LA affinity for AAGP increases with hydrophobicity and decreases with protonation.[73] Extent of protein binding increases with increasing concentrations of AAGP. Protein binding and AAGP concentrations decline during pregnancy.[74] During longer infusions of LA, concentrations of serum binding proteins progressively increase.[75] There is considerable first-pass uptake of LAs by lung. Ester LAs undergo rapid hydrolysis in blood, catalyzed by pseudocholinesterase.[52] Procaine and benzocaine are metabolized to *p*-aminobenzoic acid (PABA). Amide LAs undergo oxidative *N*-dealkylation in the liver (by cytochrome P450).[52] Amide LA clearance depends on hepatic blood flow, hepatic extraction, and enzyme function; clearance is reduced by drugs and conditions that decrease hepatic blood flow such as β-adrenergic or H_2-receptor blockers, and heart or liver failure.[52]

Toxic Side Effects of LAs

LAs can produce a long list of toxic side effects of which the following types seem most frequently associated with misconceptions, confusion, and examination questions!

Methemoglobinemia

Generations of textbooks have described the unique and predictable production of methemogloblinemia at prilocaine doses >600 mg in adults.[52] In fact, lower doses given to healthy patients produce toxic methemoglobinemia.[76] Nevertheless, perioperative methemogloblinemia in North America more commonly results from benzocaine, dehydration, or drugs other than prilocaine![77] Thus, topical benzocaine (formerly ubiquitous in endoscopy suites) has been removed from the formularies of many hospitals.

Allergy

Textbooks state (usually without providing data) that there is greater risk of allergy to ester than amide LAs, particularly to those LAs (procaine and benzocaine) metabolized to *p*-aminobenzoic acid.[52] True LA allergy is rare. Despite an apparent "allergic" or even anaphylactoid reaction, only a rare tested patient will have a IgE immune responses to preservative-free LAs.[78-80] Allergy to LAs must be distinguished from allergy to other agents (e.g. latex, antibiotics, paralytics, blood products) and also from other conditions that mimic allergic reactions.[81]

Cardiovascular (CV) Toxicity

LA-associated death (after cocaine or tetracaine topical anesthesia) first was formally studied by a national commission in the 1930s. After >80 years many important, fundamental issues remain unsettled including: 1. What is the mechanism(s) of LA CV toxicity? 2. Do all LAs produce CV toxicity by a common mechanism(s)? 3. Which animal model best mimics clinical LA systemic toxicity (LAST)?[82,83] 4. Has the introduction of ultrasound reduced the risk of LAST?

As previously mentioned, the specific Na_v channel forms and LA binding are different in the heart than in peripheral nerves.[84,85] "State" specific binding may explain how relatively low blood concentrations of LAs that have no effect on nerve conduction can have major positive or negative effects on the heart. "Slow" LA binding to Na_v channels in the inactivated state occurs at relatively low LA concentrations and is likely of greater importance when LAs serve as class I antiarrhythmics or produce LAST than as an explanation for how LAs produce conduction block of peripheral nerves.[85] The greater concentrations typically used for regional anesthesia are sufficient even for LA binding and inhibition of "resting" as well as "open" or "inactivated" Na_v channels.

Laboratory studies provide insight into why bupivacaine appears to have a greater propensity to produce severe LAST than most other LAs. Bupivacaine binds cardiac Na_v channels more avidly and longer than lidocaine.[3-5] R(+) isomers bind cardiac Na_v channels more avidly than S(-) isomers (levobupivacaine and ropivacaine).[86] When applied to isolated cardiac Nav1.5 channels bupivacaine produces concentration- and voltage-dependent inhibition. It promoted inactivation and impaired activation of Nav1.5.[87] LAs inhibit cardiac conduction with the same rank order of potency as for nerve block.[88] LAs produce myocardial depression. As noted earlier, LAs bind and inhibit cardiac Ca and K channels, but at concentrations greater than needed to inhibit Na_v channels.[2,89] LAs bind β-adrenergic receptors and antagonize epinephrine stimulation of adenylyl cyclase.[90,91] LAs produce CNS excitation, tachycardia, and hypertension at lower doses and concentrations than those associated with cardiac depression.[52]

Different LAs have differing patterns of CV toxicity. In whole animal experiments, most LAs will only produce CV toxicity at blood concentrations greatly exceeding those producing seizures; however, experimental and clinical reports suggest a reduced margin of safety for bupivacaine compared to other agents.[52,92] In dogs, supraconvulsant doses of bupivacaine more commonly produce arrhythmias than supraconvulsant doses of ropivacaine or lidocaine.[92] Animals premedicated with midazolam or diazepam (or receiving general anesthesia) may manifest bupivacaine LAST as CV collapse without convulsions.[93] In animals, the rank order of potency for cardiac toxicity appears to be the same as for nerve block.[94,95] Both programmed electrical stimulation and epinephrine elicit more arrhythmias with bupivacaine than with lidocaine or ropivacaine.[96-98] Having received LAs to the point of extreme hypotension, dogs given lidocaine could be resuscitated, but required continuing infusion of epinephrine to counteract LA-induced myocardial depression. When extreme hypotension was produced by bupivacaine or ropivacaine, some dogs required only electrical defibrillation; others could not be resuscitated using the full ACLS armamentarium.[96-98] Studies in pigs also show that bupivacaine (compared to lidocaine) may have a greater relative potency for producing both arrhythmias and myocardial depression, but that the potency ratio for producing arrhythmias is much greater (16:1) as compared to their relative potency at producing nerve block .[99]

What to do about the recreational cocaine user presenting for surgery?

Many patients present for surgery with a history of cocaine use. Cocaine is well known to produced cardiac toxic effects including arrhythmias. Cocaine persists for a relatively short time in the blood stream; however, many "drug screens" test for its metabolites and they can be detected in blood and urine far longer. It seems reasonable to require

that the patient not have injested cocaine in close proximity to elective surgery. Studies suggest that there will be almost no detectable cocaine 6 hrs after either smoking or injecting it.[100,101]

Chondrotoxicity

In recent years there has been increasing use of LA infusions into surgical wounds for postoperative pain control. As previously mentioned, some patients who received LA infusions into joint spaces have developed chondromalacia, with litigation against physicians and suppliers of LAs and wound infusion devices. Increasing evidence documents adverse effects of LA infusions on articular cartilage leading to a growing consensus against exposure of articular cartilage to increased concentrations of LAs.[41]

Treatment of LA Toxicity

Serious degrees of methemoglobinemia are treated with oxygen and methylene blue 1 mg/kg IV. Anaphylactoid reactions may require epinephrine, fluid resuscitation, and steroids. Minor LA reactions usually will terminate spontaneously. Severe LAST requires active treatment in which adherence to a check-list protocol will likely increase patient safety.[102] LA-induced seizures require maintenance of adequate ventilation and oxygenation and protection of the patient from injury. Seizures may be terminated with IV midazolam (0.05-0.10 mg/kg), propofol (0.5-1 mg/kg), or *perhaps* intravenous lipid.[3,83,103,104] If LA intoxication produces hypotension without cardiac arrest it may be treated by infusion of vasopressors (phenylephrine 0.5-5 µg/kg/min, norepinephrine 0.02-0.2 µg/kg/min, or vasopressin 2-20 units IV). A survey of academic anesthesia departments in the USA confirmed inadequate understanding and no consensus regarding resuscitation drugs for LAST.[106] I hope that the situation has improved. In any case I recommend that LAST be treated per the ASRA guidelines[104] Epinephrine may be required, but it should be administered in incremental, just sufficient doses to avoid toxic side effects.[105] With unresponsive LA CV toxicity, IV lipid should be administered and cardiopulmonary bypass (or other forms of mechanical cardiopulmonary support) should be considered.[107-109] Animal experiments and human case reports describe the ability of lipid infusion to resuscitate animals from bupivacaine LAST, even after "conventional" resuscitative efforts (including ventilation with oxygen, chest compressions, and ACLS drugs) have proven unsuccessful.[107,108] The prevailing explanation for lipid's mechanism of action is that LA diffuses from the CV system and is absorbed into a "lipid sink." There is also evidence that certain lipids may antagonize the binding of LAs to the Na_v channel.[110] Experimental evidence is conflicting whether long-chain lipids (e.g. Intralipid™) are preferable to mixed long- and medium-chain lipid emulsion.[111,112] Lipid has been used to treat overdoses of lipophilic compounds other than LAs such as bupropion and lamotrigine, and has also been used for lidocaine overdose in the critical care unit.[113] Lipid resuscitation is advocated for treatment of poisoning by other xenobiotics including tricyclic antidepressants and verapamil, but the data supporting lipid efficacy are much more robust for local anesthetic toxicity than for any other drug class.[114] Some now speculate that lipid therapy should be initiated for incipient LA toxicity (e.g. for CNS symptoms) before conventional drug treatments. Toxic side effects of lipid resuscitation have been reported only rarely, but massive doses can lead to lipemia, hypersomnolence, tachypnea, lactic academia, and difficulties with interpretation of laboratory values.[115]

Summary

After >125 years the place of both LAs and regional blocks in medical practice remain secure. Some features of LAs and regional anesthesia are well understood. Peripheral nerve blocks almost certainly result from LA inhibition of Na_v channels in axonal membranes. On the other hand, the relative clinical potency of the various LAs remains poorly defined,[116] and the mechanisms of spinal and epidural anesthesia remain unclear. The clinical importance of LA binding to TRPV1 channels remains speculative. The precise mechanism by which LAs produce CV toxicity is not clear and there may be more than 1 mechanism: more potent agents (bupivacaine) have greater propensity for arrhythmias and conduction disturbances than less potent agents (lidocaine); all LAs at increased concentrations will produce myocardial depression. Avoiding LAST is clearly preferable to treating it, however effective lipid resuscitation may be. Finally, ultrasound guidance and good technique have likely reduced (but not removed) the risk of LAST during regional nerve blocks.[117]

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Central Line Insertion: Current controversies and best practices in 2017

Avery Tung, M.D. FCCM **Wilmette, IL**

Introduction:

Recent improvements in the process of central line insertion are an example of how medical quality and safety can improve dramatically over just a short time. Driven by a decreasing number of clinical opportunities for teaching line insertion, awareness of the role of medical error in patient outcomes, and a desire to minimize preventable complications, clinicians of all specialties have revolutionized the avoidance, detection, and treatment of central line complications including failed insertion, pneumothorax, air embolism, arterial cannulation, catheter related bloodstream infections, and retained guide wire. As an example, the Pubmed search term "central venous catheter" returned 70 entries in 1990 vs 971 in 2015. As a result of new technology, systematic optimization, safety culture, and a belief that lower complication rates are possible, central line insertion has become markedly safer even as the number of central lines inserted by anesthesiologist decreases.

Three advances in line insertion stand out. The first is the widespread adoption of high fidelity 2 dimensional ultrasound devices for vein localization and dynamic needle guidance. These devices have enabled clinicians to define central vein anatomy with greater accuracy than by landmark methods, and provided inserters with real time guidance during line insertion. Nearly all studies now agree that use of ultrasound for vein identification and needle guidance during insertion greatly facilitates the actual cannulation process (2-4), and a 2015 Cochrane review (5) underscored the value of ultrasound for increasing the chance of first stick success, decreasing the risk of arterial puncture and hematoma formation, and reducing the time to successful line insertion.

The second strategy contributing to safer central line insertion has been the development of organized, start-to-finish systematic processes for placing central lines. Symbolized by central line checklists, supply carts tailored to line insertion, and EMR pathways, this conceptual shift has transformed the process of line placement from "just another clinical chore" into a technical, complex task. Considerable evidence suggests that approaching line insertion using a central line checklist can meaningfully reduce the incidence of central line bloodstream infections. In addition to the seminal 2006 report of reduced central line infections with checklist use (6), large national databases also suggest dramatic reductions in central line infections (7) when specific processes are used. Emerging data suggest that, of the checklist items commonly used, avoiding the femoral site and removing unnecessary lines have the greatest impact on line infection rates (8).

The third advance is an increased focus on higher fidelity technical training for line insertion. In many large teaching hospitals, historic "see one do one" approaches have been supplanted by computer based training programs and/or hands-on simulation. With these advanced educational approaches, novices can become familiar with insertion hardware, patient anatomy, and ultrasound visualization, refine their sterile technique, practice and rehearse rescue or troubleshooting strategies all without adverse effects on actual patients. Existing evidence suggests that such high fidelity simulation can reduce complications (9), and improve overall insertion success (10).

Partly as a consequence of the benefit of these interventions, numerous medical specialty societies have responded to this increased focus on central line safety and evolution in insertion techniques. The American Society of Anesthesiologists (ASA) (11), American College of Surgeons (12), British National Institute of Clinical Excellence (13), Australian Clinical Excellence Commission (CEC) (14), Swedish Society of Anaesthesiology and Intensive Care (15), Asia Pacific Society for Infection Control (16), and the Centers for Disease Control (17) have all issued recommendations regarding best practice for some aspect of central line insertion. This talk will review existing literature (including these guidelines where relevant) with respect to central line insertion, identify best practice where applicable, and briefly address specific complications of line insertion.

Pre-insertion

a. Indications

A full discussion of indications (and contraindications) for central line placement are beyond the scope of this talk. Two trends in clinical practice are worth noting. The first is a decreasing emphasis on central venous access for

hemodynamic monitoring purposes. Neither central venous pressure measurement nor Swan Ganz catheterization, for example, clearly improve outcomes when used for hemodynamic monitoring (18,19) and PA catheter use is declining (20). The second is the increasing use of peripherally inserted central access (PICC) lines and tunneled lines for intravenous infusions. In fact, radiologists now place the majority of central lines in the United States (21)

b. Location and resource preparation:
If time permits, surveying the anticipated site of central line insertion with ultrasound can identify anatomical issues that may complicate placement. "Pre-scanning" can be particularly useful in complex patients with other venous hardware, previous central lines, prior neck surgery and/or venous thrombosis. Unanticipated abnormalities in the size/location of the target vein, hematomae or clot, and/or foreign bodies are all identifiable with ultrasound. In one study of ultrasound surveillance, the internal jugular vein could not be visualized in up to 2.5% of patients (2). For the internal jugular site, prescanning may permit positioning the head to maximize lateral separation of the carotid and internal jugular vein. Increased head rotation frequently increases carotid/internal jugular overlap (22), raising the risk of inadvertent carotid puncture.

Although not evidence-based, Both ASA and CEC guidelines recommend basic levels of ancillary support for central line insertion. An environment that permits use of aseptic techniques, a trained assistant, adequate space and lighting, access to a handwashing sink, monitoring equipment for ECG, BP, and pulse oximetry, and immediate access to resuscitation equipment and drugs are considered basic support requirements for line insertion.

c. Site Selection:
Historically, femoral insertion sites have been considered at higher risk for infection than either IJ or subclavian sites, and one element of the original insertion bundle was avoidance of the femoral site (6). However, more recent data suggest little difference in infectious risk between sites (23). A 2012 Cochrane review (24) found no site specific difference in catheter-related blood stream infections or colonization and also observed "no overall differences in catheter-related complications between the subclavian and internal jugular sites". Declining infection rates with femoral catheters due to improved management (25) may partly explain this narrowing in infection risk among central cannulation sites.

The Cochrane review also found more thrombotic and mechanical complications with the femoral (vs subclavian) site but fewer mechanical complications than the internal jugular site and no difference between subclavian and internal jugular insertion sites with respect to mechanical or thrombotic complications. A more recent study (26) found greater thrombotic risk in the internal jugular than the femoral position, however.

The largest *randomized* analysis of line sites and complications is the 2015 "3Sites" study, published in the New England Journal (27). This multicenter trial randomized 3,471 insertions to the subclavian, femoral, or internal jugular sites and found a higher incidence of their prespecified composite outcome (vein thrombosis & CLABSI) in the femoral and IJ sites when compared to subclavian. The 3site authors also found a higher incidence of mechanical complications in the subclavian group…primarily pneumothorax. Although variation in line insertion techniques among sites (twice as many IJ lines were inserted under ultrasound than subclavian or femoral…and the failure rate for subclavian was twice as high as for IJ), and an unusually high CLABSI rate (>1:1000 catheter days) make the study difficult to generalize, it does provide a window into a relatively current ICU practice.

With respect to other aspects of line site selection, anatomy favors the right vs the left internal jugular insertion site, due to the larger diameter and straighter course of the right IJ, the lower right pleural dome, absence of the thoracic duct, and ease of access for the right handed operator (28, 29). Although existing evidence does not favor internal jugular over subclavian approaches, multiple case reports describe aortic injury, hemothorax, and tamponade with subclavian central venous catheterization. In addition, literature reviews suggest slightly higher risk for arterial puncture with the right subclavian approach, possibly due to kinking of the guidewire during vessel dilation (29). One 2002 (pre-ultrasound) meta-analysis (30) assessed 6 comparative trials with >2000 internal jugular and subclavian catheters and found more arterial punctures with the jugular approach, more malpositions with the subclavian approach, and no difference in hemo or pneumothoraces.

Changes in clinical practice may also affect line site selection. Most prominent among these is the use of ultrasound. Because of anatomical considerations, ultrasound imaging is better for internal jugular than for subclavian insertion. This slight advantage to internal jugular line placement may affect clinical decision making, particularly when patients are anticoagulated or have a history of difficult line insertion. In addition, the tendency for large bore subclavian lines to result in subclavian vein stenosis (31) has caused current CDC guidelines and the National Kidney Foundation to recommend against subclavian dialysis access (32). The increasing use of peripherally placed central catheters (PICCs) have also increased awareness of thrombotic complications as malignancy, TPN, left sided placement, and renal failure are risk factors (33). NKF-KDOQI now cautions against PICC lines ipsilateral to planned dialysis access sites due to concern for thrombosis (31).

Taken together, these data and guidelines suggest the following "best practice" approach to line site selection:

1. Identify available sites. If possible, avoid sites with prior surgery, known thrombotic complications, broken/infected skin, or existing hardware (such as transvenous pacemakers). Be aware that case reports identify the left IJ site as more complication prone than the right IJ, suggest a higher likelihood of aortic injury/tamponade with subclavian vs internal jugular approaches, and imply that the more tortuous path of the right subclavian approach may predispose to aortic injury due to guidewire kinking.
2. Prioritize the femoral site LAST for thrombosis and infectious control reasons, particularly if the duration of the line is expected to be long. Although existing data find no clear evidence of increased infectious risk in the femoral position, these results may be due to shorter line durations or better dressing technology. If access requirements are emergent, however, femoral access followed by relocation to a less infection prone site after stabilization is reasonable
3. Scan available sites to identify potential barriers to site insertion
4. If placing a large-bore introducer, consider the smaller size and more variable location of the left IJ, and risk of subclavian stenosis with large bore indwelling catheters as potential decision factors.
5. Recognize the increased thrombotic risk of PICC lines, particularly in renal failure patients and when larger bore, placed on the left side, or used for TPN.

e. Aseptic technique

While existing literature is unable to quantify the contribution to reducing central line infections from specific aseptic activities, "bundles" of activities performed together have been extensively and empirically tested. Elements of such bundles include cap, mask, sterile gown and gloves, and handwashing prior to performing the procedure. The most prominent of these "bundles" is that used in the Michigan "Keystone" project, which combined inserter strategies (cap, mask, handwashing, sterile gown and gloves) with specific patient preparation (chlorhexidine skin prep and full body sterile drape (6)) and found a sustained reduction in line infection rates.

Among bundle components, avoiding the femoral site and removing unneeded lines have the greatest impact (8). But even partial bundle compliance reduces infection rates, and compliance is worst for avoiding the femoral site (34, 35). These data suggest that specific elements of a line insertion "bundle" may not be as important as whether a bundle is used at all.

With respect to skin preparation, chlorhexidine and alcohol has largely supplanted Povidine-Iodine due to controversial guideline pressure (36). The largest trial to date comparing the two strategies finds Chlorhexidine superior for CLABSI prevention, but that it also caused more skin reactions (37). A 2016 Cochrane review found weak evidence for the superiority of Chlorhexidine when compared to Povidine Iodine (38). Note that the package insert for chlorhexidine/alcohol recommends a, "back and forth" scrubbing application pattern for 30 seconds rather than the "inside to outside' circular pattern used for Povidine Iodine. This 'scrubbing" strategy is advocated to penetrate the first 5 cell layers where 80% of skin flora reside (39).

With respect to antibiotic-impregnated central lines, a 2013 Cochrane review (40) found a reduction in catheter colonization and related bloodstream infections only in the ICU and no effect on mortality. A 2016 trial of chlorhexidine impregnated lines also found no reduction in CLABSI with chlorhexidine impregnated lines (41) CDC guidelines recommend use of impregnated catheters only for prolonged use, or if a comprehensive strategy to reduce infection rates does not work.

Insertion

a. Patient position

Existing evidence suggests that abdominal compression, increased intrathoracic pressure, and Trendelenburg position increase internal jugular vein size (42). Effects of similar maneuvers on subclavian vein size are unclear (43). Nevertheless, using the Trendelenburg position where clinically feasible for both access sites reduces the risk of air embolism. When targeting the internal jugular site, current evidence suggests that head rotation should be limited as increasing head rotation increases overlap between the internal jugular vein and carotid artery (22). Evidence suggests modest improvements in subclavian vein size with the head in the neutral position (43).

Although the choice between Seldinger and modified Seldinger techniques is mostly inserter preference, a small 2015 trial found fewer punctures and a higher first pass success rate with the Seldinger technique (44). In the Seldinger technique, the inserter cannulates the vein using a thin walled, hollow needle and inserts a wire through the needle and into the vein. In the modified Seldinger technique, the inserter cannulates the vein using a hollow needle which is threaded through a plastic catheter. Once blood return is obtained, the plastic catheter is threaded over the needle and into the vein. The guide wire is then passed through the plastic catheter into the vein and the plastic catheter is removed. Arguments for the Seldinger technique include speed and simplicity. Arguments for the modified technique include ease of pressure transduction for venous confirmation, and a more stable platform for wire insertion for the novice. It is easy to see that local preferences, operator skill, and equipment availability likely have a greater effect on cannulation success than intrinsic aspects of each technique.

Several observational studies find that central venous access complication rates increase with the number of needle passes (45), and that more experienced operators have higher success rates (46). Based on these data, practitioners should consider changing operators or techniques if multiple passes by a single operator are unsuccessful.

All of the guidelines listed on page 1 of this handout recommend the use of ultrasound to facilitate central line insertion. Arguments against routine use of ultrasound include time, availability of equipment during emergencies, and adverse effects of improper use. One important caveat to ultrasound use is verifying needle tip position. Whether short or long axis view, identifying the tip is difficult and in short axis the tip and shaft of the needle will appear identical on ultrasound. Inexperienced operators may fail to scan distally to locate the tip, causing underestimation of the depth of needle insertion and leading to carotid puncture, pneumothorax, and other complications. Current literature finds arguments for both views (47, 48) Focusing on the ultrasound image instead of the patient during insertion may also lead to overadvancing the needle (49). Developing ultrasound skill is considered so important that CDC guidelines for prevention of central line infections consider training a category 1B recommendation and CEC guidelines explicitly state that “previous training or experience is required to use this technology effectively”. Two “clinical pearls” that may help with needle and wire visualization is maintaining a 90° angle between ultrasound beam and needle, and tilting the probe to follow the wire below the clavicle.

Although no direct evidence exists to specify how deep the wire should be inserted into the vein, reported complications from deep insertion of the wire include dislodgement and ensnarement of vena caval filters (50), entanglement in the tricuspid valve (51), and complete heart block (52). This literature suggests that best practice should avoid inserting the wire too deeply. Once the wire is inserted, a verification step is strongly recommended to verify wire location in the target vein. However, few verification strategies are validated by high quality current evidence and no comparative trials exist. Strategies to distinguish venous from arterial location with equivocal (and thus not recommended) evidence include pressure waveform analysis, color of blood, blood gas analysis, or absence of pulsatile flow. Other strategies such as fluoroscopy, continuous electrocardiography, transesophageal echo, or chest XRay have little comparative evidence, but considerable face validity. The “bicaval” TEE view of the right atrium is widely considered the most reliable guide to verifying wire location in the right atrium.

The two most commonly used strategies are ultrasound and manometry. Just as it is used to identify the vessel, ultrasound can also be used to track the guide wire from where it enters the skin to where it enters the relevant vessel. This approach, however, is not foolproof. If an error is made in identifying the correct vessel then verification using ultrasound will likely fail to catch that original error. In addition, ultrasound may not be able to track more than 5cm into the thoracic cavity. Guidewires that pass completely through the vein and end up in the subclavian artery may escape ultrasound-based verification.

The strongest published evidence for verifying wire location in the vein is manometry. With this technique, a length of IV tubing is attached to an IV catheter or needle located inside the vessel in question. The pressure in the vessel is then measured either by holding the tubing vertically and visualizing the height of the column, or by connecting the tubing to a pressure transducer. In a 2009 retrospective review, 9,348 central venous catheters placed during a 15 year period using manometry to verify venous location of the wire (53). No cases of dilator placement into adjacent arteries were noted, and the authors calculated that use of manometry prevented up to 56 possible arterial dilations.

The choice of verification technique depends in part on cannulation technique. With the Seldinger technique, use of manometry to verify wire placement must be performed with the needle tip manually stabilized while in the vein or by inserting the wire and switching over to a plastic catheter. It is easy to see that this approach requires a high degree of manual dexterity, and may result in loss of access or air embolism, particularly when access is difficult or the patient is breathing spontaneously or moving. In contrast, with the modified Seldinger technique the inserter threads a plastic catheter over the hollow needle into the vein. Manometry can then be performed via this catheter.

Overall, existing evidence is insufficient to dictate a 'best practice". Nevertheless, case reports, observational trials, clinical experience, and expert opinion can be integrated to recommend a reasonable practice with respect to the insertion process:
1. Because the consequences of arterial puncture are significant, verification that the target vein has been cannulated (vs the artery) is strongly recommended by ASA and CEC guidelines
2. Blood color, waveform analysis, and/or pulsatility are NOT recommended due to the high likelihood of error
3. Case reports and observational trials support the use of fluoroscopy, catheter tip electrocardiography, or TEE
4. The two verification strategies with the greatest degree of overall support are pressure transduction of the target vessel (manometry) and ultrasound imaging of the catheter inside the target vessel.
5. Choice of verification technique should depend on operator experience and technical issues. Because use of manometry with the Seldinger "wire through needle' technique is technically more difficult than with the modified "catheter over needle" Seldinger approach, consider using ultrasound verification with the Seldinger technique.

Some controversy exists with respect to tip position. While tip location in the right atrium predisposes to perforation and tamponade (54), cadaver studies suggest that the pericardial reflection can reach as high as the middle third of the superior vena cava (55). In addition, a "high" catheter tip from the left subclavian or IJ site is prone to thrombosis/malfunction (56) and may form an acute angle to the SVC and predispose to perforation (57). Verifying that the tip of the line does not protrude below the bottom border of the right mainstem bronchus is helpful in preventing atrial location (58). Although ASA guidelines are silent, CEC guidelines provide a table to specify insertion depth as a function of patient height and insertion site.

Complications and aftercare

The list of complications referable to central line insertion is large. These include arterial puncture, hematoma, hemothorax, pneumothorax, aortic injury, vena caval or atrial perforation, tamponade, intrathecal insertion, guide wire loss, thoracic duct damage, arrhythmia, and catheter-related infection. A 2003 New England Journal review estimated the incidence of arterial puncture as 6-9% for the IJ site and 3-5% for the subclavian site, and the incidence of pneumothorax as 0.1-0.2% for IJ and 6 to 11% for subclavian sites (59). With ultrasound, the incidence of arterial puncture is now ~1% for the IJ site.

A 1970- 2004 closed claims analysis of central line complications found 110 claims for injuries related to central lines (60). The most common were wire/catheter embolus (N=20), followed by tamponade, carotid artery puncture/cannulation, and hemothorax/pneumothorax. Post-insertion best practice should thus include maintaining a high degree of suspicion for the possibility of injury due to line insertion.

Other elements of central line aftercare includes attention to infection prevention. Daily attention to the ongoing need for central access, and prompt removal if the line is no longer necessary can clearly shorten line duration and reduce infectious complications. Existing literature recommends against routine replacement of central venous catheters (61), against routine use of antibiotic ointments (62), and against routine wire guided line exchange (61).

Summary

Recent advances in central line insertion techniques, increased attention to central line complications, and improved training strategies have dramatically improved central line insertion. For many aspects of line insertion, best practices are beginning to emerge and include an organized, systematic approach to inserter training and line insertion, consistent aseptic preparation of the patient and inserter, use of static and dynamic ultrasound when feasible, evidence based site selection, verification of wire position, localization of the catheter tip, and post-insertion maintenance.

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Postpartum Hemorrhage: How to Prepare for It, How to Prevent It, and What to Do When Blood is Pooling on the Floor

Jill Mhyre, MD **Little Rock, Arkansas**

The learner will: 1) List options available to control and mitigate the consequences of obstetric hemorrhage; 3) Discuss how contemporary transfusion practices apply in the obstetric setting; and 3) Draw from published guidelines and protocols to inform both individual clinical practice and systems solutions to prepare for these emergencies.

Definitions

Postpartum hemorrhage is defined by ACOG as cumulative blood loss ≥1000 mL, regardless of mode of delivery. Blood loss ≥500 mL following vaginal delivery should prompt action to monitor and control blood loss. The risk for adverse health outcomes accumulates with **persistent postpartum hemorrhage,** when bleeding exceeds 1000 mL and persists despite the use of first-line uterotonics and uterine massage,[1] particularly if bleeding is accompanied by signs or symptoms of hypovolemia.[2] The National Partnership for Maternal Safety recently defined indicators of **severe maternal morbidity** as ICU admission or transfusion with 4 or more units of blood products, and recommended that women with these indicators receive multidisciplinary review for the purpose of identifying opportunities for systems improvement.[3] Massive blood transfusion has been defined as >10 u blood products transfused during the hospitalization for delivery[4] or as erythrocyte transfusion >3 u/hour.[5]

Commented [MJM1]: ACOG 2015, **https://tinyurl.com/y9nrcc75**

https://www.acog.org/-/media/Departments/Patient-Safety-and-Quality-Improvement/2014reVITALizeObstetricDataDefinitionsV10.pdf?dmc=1&ts=20170616T1237284451

Etiology

Primary postpartum hemorrhage develops within 24 hours of delivery and is due to uterine atony, retained placenta, genital tract trauma, placenta accreta, increta or percreta, uterine inversion, or coagulopathy. Coagulopathy may be inherited or result from a range of disorders in pregnancy, with amniotic fluid embolism being the most severe.[6] *Secondary postpartum hemorrhage* is relatively infrequent, develops over 24 hours after delivery, and is ascribed to subinvolution of the placental site, retained products of conception, infection, or inherited coagulation defects.

Epidemiology

Postpartum hemorrhage complicates at least 3% of all deliveries, and appears to be increasing in frequency.[7,8] Approximately 3% of women receive any blood products; many are transfused to treat normal blood loss in the setting of antepartum anemia. Hemorrhage accounts for close to half of obstetric intensive care unit admissions,[9] and 38% of cardiac arrests during the hospitalization for delivery.[10]

Uterine atony underlies 80% of all cases of postpartum hemorrhage.[7] Population-level factors driving the increasing frequency of uterine atony include: 1) increasing population prevalence of obesity, multiple gestation, and advanced maternal age; 2) increasing inductions of labor;[11] and 3) increasing cesarean deliveries, from 21% of all births in 1997 to 32.0% in 2015.[12] Unrelenting uterine atony leads one-third of all peripartum hysterectomies.[13] Uteroplacental inflammation (e.g., chorioamnionitis, vasculitis, funisitis, endometritis, and cervicitis) appears to be a major contributor to uterine atony that is sufficiently severe to require peripartum hysterectomy.[14]

Placenta accreta with or without placenta previa is the leading cause of massive blood transfusion.[4] Accreta leads to approximately half of all peripartum hysterectomies, and rates have increased in conjunction with the burgeoning population of pregnant women with prior cesarean deliveries.[4]

Historically, hemorrhage was the leading cause of maternal death in the United States, but accounts for 11% of the total, or 1.8 maternal deaths per 100,000 live births in the United States.[15] The majority of hemorrhage-related deaths are preventable.[16-19]

Anticipated Postpartum Hemorrhage

Even with the physiologic anemia of pregnancy, a hematocrit less than 32% should be treated to reduce the risk of peripartum blood transfusion (e.g., oral or intravenous iron). In addition, three groups need special antenatal preparation: 1) women with abnormal placentation; 2) those with inherited coagulation disorders; and 3) those who refuse blood products.

Abnormal Placentation

With placenta accreta, the decidua basalis (i.e., the decidual basal plate) is absent, and the basal plate of the placenta adheres to a floor of uterine myometrium. With placenta increta, chorionic villi invade into the myometrium, and with percreta, the placenta penetrates the uterine serosa, and may even grow into other pelvic structures, most commonly the bladder. Placental location mediates the relationship between prior cesarean and risk of accreta. When placenta previa is present, the incidence of a morbidly adherent placenta increases from 3% among primary cesarean deliveries, to 11%, 40% and >60% after one, two, and three or more prior cesarean deliveries, respectively.[20] When the placenta does not involve the cervix or lower uterine segment, accreta is relatively rare (1%), even with multiple prior cesarean deliveries.[20]

Intrapartum blood loss is difficult to predict.[21] Antenatal recognition and controlled surgical delivery improve outcomes.[22-25] Accreta is often evident on the anterior surface of the uterus, and in such cases, as long as the mother and fetus are stable, it may be possible to close the abdomen and transfer the patient to a center of excellence for planned cesarean hysterectomy.[26] Ultrasonography to locate the placenta and evaluate for markers of placenta accreta is recommended for every woman who has undergone prior uterine surgery, or found to have a low-lying placenta on the routine first or second trimester ultrasound.[27,28] Magnetic resonance imaging (MRI) may help to confirm the diagnosis when ultrasound is inconclusive, and define the extent of invasion into surrounding organs in the case of placenta percreta.[27] Women with a diagnosis of abnormal placentation based on ultrasonography are more likely to require blood transfusion and peripartum hysterectomy, and require more units of blood products transfused, when compared with women without definitive ultrasound findings.[21,29]

Surgical management is directed towards delivering the neonate, then closing the uterus with the placenta left *in situ*, followed by planned peripartum hysterectomy.[30] For women who desire fertility preservation, prophylactic uterine artery balloon catheters, stepwise uterine devascularization, pelvic vessel ligation or embolization, uterine compression sutures, and/or postpartum methotrexate may facilitate hemostatic control and placental involution.[31]

Optimal management by the anesthesiologist ensures sufficient intravenous access and blood products to respond to massive hemorrhage, hemodynamic and hemostatic monitoring capability (e.g., central venous and peripheral arterial access), sequential compression stockings to prevent venous thromboembolism, padding and positioning to prevent nerve compression injury, warming devices to ensure normothermia, standard preoperative antibiotic prophylaxis in the hour prior to surgical incision and repeated if surgery is prolonged (i.e., ≥3 hours) or if heavy bleeding occurs.[27] Given inaccuracy of models to predict total blood loss in these cases, the total number of recommended blood products to prepare depends on institutional capacity to maintain ongoing supply in the face of massive hemorrhage.[21,32] Aggressive uterotonic administration, cell-saver auto-transfusion, massive transfusion management, and electrolyte and hemostatic measurement and management are discussed below.

Combined spinal epidural (or standard epidural) anesthesia allows the mother to be awake for the delivery, may be extended for prolonged surgery, and is associated with improved neonatal Apgar scores at birth.[33] General anesthesia is preferred for cases with massive transfusion in the event of airway edema, fluid overload with pulmonary edema, or transfusion associated lung injury (TRALI). The decision about the primary anesthetic technique will weigh the magnitude of anticipated blood loss, the extent of the operative plan, the availability of additional anesthesia staff to assist with an unplanned conversion to general anesthesia, and the anticipated risk of a difficult airway.

Prophylactic embolization catheters may be inserted preoperatively into the anterior internal iliac or uterine arteries to facilitate balloon inflation or embolization immediately following delivery of the infant.[27] Efficacy has not been verified by randomized controlled trial.[34] While these catheters may be indicated for women who desire fertility preservation, and in women with extensive or unrespectable placenta percreta, routine use is not recommended by the Society for Maternal-Fetal-Medicine due to lack of demonstrated efficacy as well as potential complications including arterial injury, abscess, tissue infection and necrosis.[27] Epidural anesthesia should be initiated prior to femoral sheath insertion, to facilitate optimal positioning for both procedures and patient comfort.

Inherited Coagulation Disorders

Von Willebrand disease, hemophilia A and B, and factor XI deficiency account for approximately 90% of inherited bleeding disorders.[1,35,36] Inherited platelet disorders (e.g., Bernard Soulier Syndrome, Glanzmann thrombasthenia) are rare. Given the clinical heterogeneity within each diagnosis, consultation with a hematologist and blood bank personnel will help to clarify optimal management for each patient. Sixteen percent of women who have von Willebrand disease will experience PPH within 24 hours of delivery, and 29% will experience delayed postpartum bleeding.[37]

Jehovah's Witnesses and other women who refuse blood products

Antepartum consultation should review a comprehensive list of blood products, alternatives, and blood conservation strategies to determine acceptability of each intervention for the patient.[38] Antepartum iron and erythropoietin are often acceptable ways to optimize hematocrit prior to delivery, aiming for a hematocrit ≥35%, and may be continued postpartum in the event of significant blood loss.[39,40] Neuraxial anesthesia with a catheter-based technique may reduce intraoperative blood loss; furthermore, an awake patient may change her mind in the face of impending death. Prophylactic administration of tranexamic acid may have a modest effect on cumulative blood loss (reducing blood loss by <150 mL) if administered early in the event of hemorrhage.[41]

Commented [MJM2]: AWOMAN trial

Volume replacement with crystalloid or colloid can decrease viscosity of the blood and thereby improve peripheral perfusion and minimize cardiac work. However, excessive crystalloid resuscitation can contribute to dilutional coagulopathy and decreased oncotic pressure. Cell-saver autotransfusion is discussed below, and a continuous circuit technique is often acceptable for patients who would otherwise refuse blood products.[40,42] In the event of massive blood loss and profound anemia (hgb ≤4 g/dL) prolonged postoperative sedation, intubation, thermoregulation, and paralysis may be required to limit oxygen consumption while erythropoietin and iron are used to restore the patient's red cell mass. Erythropoietin requires 48-72 hours for a significant reticulocyte response in peripheral blood, and 10-14 days to increase hemoglobin levels. Laboratory testing should be minimized using pediatric tubes and finger-stick testing where possible.[39]

Risk stratified blood product preparation

Blood transfusion is rare following elective cesarean delivery (<1%), but risk is increased among women with antenatal anemia, placenta previa, or multiple gestation pregnancy, particularly when multiple risk factors present in combination.[43] Systems to collect a blood specimen 1-3 days prior to planned Cesarean delivery may reduce unnecessary surgical delays.[44,45] Federal law requires the use of a sample less than 3 days old for all pretransfusion blood compatibility testing in pregnant or recently delivered women (http://goo.gl/3EUGPw).

Risk factors for blood transfusion may be evident before delivery (e.g., previa), on admission to the labor and delivery unit (e.g., severe anemia), at the end of the first stage of labor or upon transfer to the operating room for unplanned cesarean (e.g., chorioamnionitis), or on transfer to postpartum care. The Association of Women's Health Obstetric and Neonatal Nurses (AWHONN) published a structured risk assessment tool for nurses to apply at each time point, paired with anticipatory actions (www.pphproject.org). The AWHONN list is sensitive, but not very specific to predict hemorrhage and/or blood transfusion. The following list focuses on the most significant risk factors for blood transfusion and prolonged blood product preparation.[43,46,47]

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Table 1. Blood product preparation based on the level of risk for peripartum blood transfusion

Recommendations AND Indication	Conditions

Prepare ≥2 units PRBC
Indication: Transfusion risk > 10%
	• Severe anemia (antepartum Hct <25%)
	  ○ Mild anemia (Hct 25.1-29.9%) + other risk factors
	  ○ Thrombocytopenia (platelets <100k) + other risk factors
	• Multiple gestation + other risk factors
	• Active bleeding
	• History of previous severe postpartum hemorrhage
	• Coagulation disorder including HELLP
	• CD for placenta previa, IUFD, or chorioamnionitis

Indication: Prolonged T&S Prolonged T&C	• Positive antibodies on T&S (Anti-D is usually Rhogam†) • History of difficult crossmatch • Sickle cell disease requiring extended crossmatch
Prepare for Massive Transfusion‡ • 4-20 units PRBC • 4-20 units FFP • 1-4 platelets (5-pk)	• Maternal history of prior Cesarean deliveries **AND** a placenta overlying the uterine scar or placenta previa • Imaging indicates placenta accreta, increta, or percreta • Planned cesarean hysterectomy

CD = cesarean delivery; FFP = fresh frozen plasma; Hct = hematocrit; HELLP = hemolysis, elevated liver enzyme, low platelet syndrome; PRBC = packed red blood cells

† Extra time is needed to discriminate between anti-D antibodies due to RhoGAM® and any additional antibodies that could interfere with a type and crossmatch.[48]
‡The exact number of units determined by a patient-specific assessment of risk for massive blood loss, and institutional resources to rapidly procure additional blood products.[21,32]

Unanticipated Postpartum Hemorrhage

System Factors
Clear multidisciplinary guidelines and regular skills training (multidisciplinary drills) reduce the incidence of massive PPH and hemorrhage-related morbidity,[49-53] and are recommended for all units by the National Partnership for Maternal Safety.[54] Simulation-based training for obstetric hemorrhage encounters can reveal specific management deficits, and thereby facilitate targeted quality improvement and staff education.[55]

Accumulating evidence suggests treatment delays increase risk for severe obstetric hemorrhage and hemorrhage-related maternal death.[16,56,57,58] Bundling personnel, equipment, and drug resources ensures rapid and reliable delivery to the bedside.[54] Group paging systems can simultaneously request an entire Obstetric Medical Emergency Team.[59,60] Likewise, an obstetric hemorrhage cart can be used to store essential equipment.[51] An obstetric hemorrhage drug pack containing uterotonics allows for efficient retrieval in the event of an emergency. Hemorrhage drills may be used to measure the time interval from the request for uterotonic medication to administration.[54]

Obstetric hemorrhage is noted to be a particularly traumatic birth complication, regardless of the clinical outcome.[54] Patient, family, and staff support both during and after a hemorrhagic event are increasingly recognized as critical for restoring well-being, and mitigating complications such as post-traumatic stress disorder.[54]

The Staged Approach
A Unit-Wide stage-based obstetric hemorrhage emergency management plan is recommended by the National Parternship for Maternal Safety,[54] and is based on 4 stages of obstetric hemorrhage (0 through 4).

Stage 0
Stage 0 begins with delivery, and focuses on ongoing risk assessment and active management of the third stage of labor. Prophylactic oxytocin decreases postpartum blood loss, and the need for additional uterotonics;[61] controlled cord traction and uterine massage provide limited benefit above oxytocin alone.[62-64] The dose required to initiate acceptable uterine tone following cesarean delivery is lower than previously assumed, 350 milliunits for elective cesarean and 3 IU for cesarean in labor.[65,66] An initial infusion of 18 IU/hour (e.g., 30 IU in 500 mL, infused at 300 mL/hour) is effective to achieve acceptable uterine tone within 5 minutes in 90% of women undergoing elective cesarean delivery.[67-69] Alternatively, some authors recommend a 3 IU loading bolus over 15 seconds, while supporting blood pressure with phenylephrine.[70,71] In women undergoing cesarean delivery after oxytocin labor augmentation, the combination of oxytocin and ergometrine reduces the need for additional uterotonic agents when compared with oxytocin alone,[72] and may reduce the need for blood transfusion in high risk women.[73]

Universal serial assessments of cumulative blood loss, vital signs, fundal height, and uterine tone should be completed for all deliveries (http://www.pphproject.org). Accurate blood loss estimation is improved by the use of calibrated drapes, formal staff training in blood loss estimation,[74,75] and gravimetric measurements.[76] Blood contained in absorbing materials (e.g., pads, sponges) can be quantified by weight, subtracting the dry weight of each item, assuming 1 gm weight = 1 mL blood.[38,76]

Because hemorrhage is often concealed or underestimated, monitoring protocols with clear triggers to escalate care are essential.[16,38] The Modified Early Obstetric Warning System is an aggregate weighted scoring system that centers in the UK use to identify women developing critical illness.[77,78] The Maternal Early Warning System suggests close evaluation if the heart rate exceeds 120 beats per minute; late signs of hemorrhage include hypotension, narrow pulse pressure, pallor or mottled appearance, cold and clammy extremities, oliguria (<0.5mL/kg/hr), anxiety, restlessness, confusion, palpitations, dizziness, diaphoresis, and dyspnea or air hunger. An obstetric shock index (HR/SBP) >1 has been associated with postpartum hemorrhage,[79,80] and a value ≥1.4 indicates the need for urgent attention.[81,82]

Stage 1: Postpartum Hemorrahge
EBL>1000, brisk gush or boggy uterus, or multiple clots AND vital signs stable. At this point, both the anesthesiologist and the obstetrician should be notified. Monitoring intensity of both vital signs and EBL should increase. Targeted therapy includes appropriate venous access, initial fluid resuscitation, uterotonics, and analgesia

to facilitate initial obstetric interventions to investigate and control the source of bleeding. The diagnostic evaluation should address the five Ts: (1) **Tone**—uterine atony; (2) **Trauma**—lacerations or genital tract trauma; (3) **Tissue**—retained placenta; (4) **Thrombin**—abnormalities of coagulation; and (5) **Turned inside out—**uterine inversion.

Rapid intravenous infusion of oxytocin may cause peripheral vasodilation, hypotension, flushing, nausea, chest pain, myocardial ischemia, and in the face of substantial hemorrhage, cardiovascular collapse.[66] Limiting the infusion rate to ≤30 IU/hour appears to minimize serious hypotensive and ishemic effects.[83] When bleeding persists despite this maximal oxytocin infusion, second-line agents are indicated, including: 1) methergine 200 mcg IM if the patient is not hypertensive, repeated once after 15 minutes; 2) misoprostol 800-1000 mcg rectally or buccally; or 3) prostaglandin $F_{2\alpha}$ 250 mcg IM every 15-20 minutes up to 8 total doses (avoided in women with asthma). Methergine appears to be the most frequently chosen second line uterotonic, and may have superior efficacy when compared with prostaglandin $F_{2\alpha}$, based on observational data.[84,85]

Stage 2: **Continued bleeding despite stage 1 interventions AND <1500 mL cumulative blood loss.**

With **persistant postpartum hemorrhage**, it becomes very important to mobilize a full team. The patient should be moved to an operating room, large bore venous access secured, and a full panel of laboratory values sent, hematocrit, platelets, PT, and fibrinogen. Cross-match of at least 2 units of erythrocytes is usually indicated, and protocols for emergency release of blood products are recommended.[44,54] Fibrinogen <2 g/L is an early predictor of the severity of subsequent PPH.[86-88] Ongoing uterotonics, thermoregulation, antibiotic coverage, and venous thromboembolism prophylaxis should be addressed. Tranexamic acid and fibrinogen concentrate are being investigated for the early treatment of postpartum hemorrhage, and are discussed below.[89,90] Decisions about transfusion, requesting additional blood products, activating a massive transfusion protocol, converting to general anesthesia, initiating cell salvage, and establishing invasive hemodynamic monitoring depend on the ongoing state of the patient, the rate of blood loss, and the degree to which obstetricians are effective in diagnosing and controlling the source of bleeding.

Stage 3: EBL>1500, >2 u PRBC given, vital sign instability, evidence of coagulopathy, or ongoing bleeding. Stage 3 qualifies as **major obstetric hemorrhage**. Following manual exploration and repair of lacerations, stepwise escalation of surgical therapy includes D&C, intrauterine balloon (e.g., Bakri balloon), and uterine compression suture (e.g., B-Lynch, O'Leary, multiple squares), selective embolization, peripartum hysterectomy, and abdominal packing. In some cases, intraoperative manual aortic compression or cross clamping may facilitate surgical control.[91] Vacuum-induced uterine tamponade is an investigational technique to treat atony.[92] Uterine inversion requires anesthesia and uterine relaxation to facilitate manual replacement.

While a hemoglobin transfusion threshold of 7 g/dL is generally appropriate, laboratory results are inaccurate in the face of ongoing hemorrhage, and transfusion should proceed empirically without waiting for laboratory results. Failure to maintain adequate hematocrit during acute obstetric hemorrhage has been associated with end organ dysfunction.[93] Observational data suggests that hemostatic resuscitation with low transfusion ratios (FFP: PRBC and Platelet: PRBC ratios of 1:1 to 1:2) may increase survival in massively transfused trauma victims,[94] and may decrease the need for advanced interventional procedures in postpartum hemorrhage.[95] However, this evidence base suffers from survival bias. A prospective RCT in trauma patients did not demonstrate improvements in overall survival when early resuscitation with plasma, platelets, and erythrocytes administered in a 1:1:1 ratio was compared with a 1:1:2 ratio.[96] Caution is advised. Plasma and platelets are pro-inflammatory, and may increase risk of pulmonary injury (e.g., TRALI) among individuals who ultimately receive ≤4-6 units of erythrocytes. [97-99] In the absence of consumptive coagulopathy or antenatal thrombocytopenia, platelets are rarely necessary before the cumulative blood loss exceeds 5 litres.[100] Goal-directed therapy guided by TEG or ROTEM may reduce the quantity of plasma and platelets transfused and the risk of major complications, such as transfusion related acute circulatory overload (TACO).[101,102]

Although massive transfusion protocols specifically for obstetric hemorrhage have been described,[103,104] standard institutional protocols are generally appropriate, as long as the higher transfusion threshold for fibrinogen is noted (≥ 2 g/L). Effective protocols are activated by phone, allow for initial supply of uncross-matched products if necessary, and supply batches of blood products that approximate the recommended 1:1:1 ratio, with the option to request cryoprecipitate early.[105,106] Subsequent matched blood products are continuously prepared to maintain blood product availability, and the protocol is automatically discontinued once additional blood products have not been requested for at least one hour.

For massive blood transfusion, laboratory specimens (i.e., hematocrit, platelets, ionized Ca, K, PT, fibrinogen, lactate) should be sent every 30-60 minutes to establish trends. Serial coagulation tests are more helpful than single time point measurements in assessing for development of coagulopathy.[5] Additional FFP may be needed to maintain

the PT ≤1.5 times normal, platelets to maintain the platelet count over 50 x 10^9/L, and cryoprecipitate or fibrinogen concentrate 4 g to maintain the fibrinogen over 2 g/L.[86-88] Central laboratory turn-around time within 20 minutes is possible,[107] but centralized viscoelastic monitoring with point-of-care real time display is emerging as a preferred strategy to facilitate goal directed therapy.[101,102,108-111] With ROTEM, amplitude at 5 minutes (A5) on the FIBTEM assay shows strong correlation with the Claus Fibrinogen measurement.[102]

In the event of unanticipated massive hemorrhage, an interosseous needle may be rapidly inserted in the tibial plateau or proximal humerus and used to initiate fluid resuscitation while additional intravenous access is established.[112] Temporizing maneuvers include leg elevation, manual compression of the aorta at the umbilicus, and non-pneumatic anti-shock garments.[113] Permissive hypotension (MAP 50 mmHg) may help to limit bleeding, but is not well studied in the postpartum patient.[39]

Adjunctive agents:

Tranexamic acid (1 g over 10 minutes, repeated once after 30 minutes if necessary) was recently studied in the World Maternal Antifibrinolytic (WOMAN) Trial.[114] This trial enrolled 20,060 women in predominantly low and middle income countries, and found that tranexamic acid administered within 3 hours of a diagnosis of severe postpartum hemorrhage decreased hemorrhage-related mortality from 1.9% to 1.5%, with no identified increase in seizures, thromboembolic events, or end-organ injury. In high-resource settings, benefit is most likely in the setting of fibrinolysis (e.g., AFE, abruption, ROTEM lysis index at 30 min >3%). Be aware that fatal drug errors have been reported in which tranexamic acid was administered in place of local anesthetic in spinal anesthesia.[115]

Lyophylized fibrinogen concentrate 2-4 g has been reported to be helpful in coagulopathic obstetric patients.[116,117] Although derived from human serum, fibrinogen concentrate is pasteurized, available in a standard concentration, and may be reconstituted and administered rapidly in a low volume.[118] Rigorous investigation suggests that it is most likely to be beneficial with administered using goal-directed treatment algorithms for women with evidence of hypofibrinogenemia.[90,101,102]

Registries of **recombinant factor VIIa** report an overall 80% success rate to control hemorrhage when other interventions have failed, with reported doses ≤90 mcg/kg.[1,119] Temperature, acidosis, calcium, platelets and fibrinogen should be first optimized for maximal hemostatic effect. Caution is advised. Recombinant factor VIIa has been associated with a high rate of devastating thrombotic complications.[120]

Cell salvage—Over 650 published cases of obstetric patients have described auto-transfusion with blood salvaged and processed from the surgical field.[121,122] Newer machines in combination with leukocyte reduction filters have demonstrated effective clearance of fetal squamous cells, phospholipid lamellar bodies, plasma heparin, cytokines, and other coagulopathic mediators. The use of a leukocyte depletion filter has been associated with acute hypotension at the time of transfusion of cell salvaged erythrocytes.[123] Cell-salvaged blood does contain up to 2% fetal red blood cells; Rhesus-negative women require dose-adjusted RhoGAM® administration. Emergency cell salvage may be most appropriate in institutions where cell saver devices are routinely used, and dedicated technicians are available to set up the equipment.[124] Some centers may elect to limit use for women with placenta accreta or those who refuse blood products.

Reporting and Systems Learning: Post-event debriefs are short clinical team meetings conducted immediately after a patient safety event, designed to build teamwork and identify opportunities for improvement. In addition, formal in-depth multidisciplinary reviews of serious hemorrhages (≥4 units of erythrocytes transfused or ICU admission) are recommended by the Joint Commission and the National Partnership for Maternal Safety (www.safehealthcareforeverywoman.org).[54]

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Interpretation of Spinal Diagnostic Imaging Studies: Learning a Structured Approach

James P. Rathmell, M.D. **Boston, Massachusetts**

Introduction

Among the most common painful disorders encountered by pain specialists are those associated with degenerative disorders of the spine. Having a clear understanding of how and when to use spinal imaging in diagnostic evaluation and treatment planning can reduce unneeded imaging, facilitate accurate diagnosis and allow for the selection of the safest treatment approaches. Central to effective use of spinal imaging studies is adopting a structured and disciplined approach to interpretation. The aim of this brief review to provide a basic approach to interpreting spinal imaging studies that will allow pain practitioners to be more closely involved in directly using these studies in their everyday practices.

Imaging modalities

The three most common imaging modalities used in the evaluation of spinal pain are plain x-ray, computed tomography (CT) and magnetic-resonance imaging (MRI). Plain x-ray remains valuable in the evaluation of traumatic injuries, where fracture or dislocation is suspected. Plain x-ray has the unique advantage that images can be taken in various positions, including the extremes of flexion and extension, allowing assessment for dynamic instability, like that which occurs with ligamentous injury. In such cases, vertebral alignment may appear normal with the spine in a neutral position, but become displaced with flexion or extension. Plain x-ray is also helpful in assessing for spinal deformity and for the integrity of implanted spinal hardware. Computed tomography has become the preferred imaging modality for assessing patients for spinal fractures associated with trauma. CT can be done rapidly, is widely available, and demonstrates fractures well. CT is also useful in assessing the bony dimensions of the spinal canal in those suspected of spinal stenosis. Myelography, performed by placing radiographic contrast within the thecal sac and subsequent use of either plain x-ray or computed tomography is still used from time to time. This method opacifies the thecal sac and can clearly demonstrate the degree of impingement of structures on the thecal sac itself – this feature can be useful in assessing the degree of stenosis of the central canal, lateral recesses, and the foramina when plain CT and MRI findings are equivocal. MRI remains the imaging modality of choice in most instances as this modality can distinguish well among bone, soft tissue, and fluid. The three MRI sequences commonly employed as part of standard spinal imaging series include T1-weighted, T2-weighted and short tau inversion recovery (STIR) sequences. On T1-weighted images, fat appears brighter than water or bone, thus T1-weighted images are useful for assessing fat-nerve and fat-fluid interfaces. On T2-weighted images, both water and fat are bright, with water somewhat brighter. Thus T2-weighted images are useful for assessing spinal cord and spinal nerve interfaces with CSF. STIR is a T2-weighted sequence aimed at further suppressing the hyperintense fat signal. STIR images are useful for assessing for the presence of edema, which remains hyperintense (bright), particularly useful for distinguishing acute from chronic injuries. When using either CT or MRI, IV contrast should be administered when the differential diagnosis includes infection, neoplasm, inflammation, or demyelination. The characteristics of these three common MRI sequences are compared in Table 1.

Table 1. MRI sequences and appearances of various structures.

MRI Sequences	Lipid	CSF/Edema	Bone	Spinal Cord/Nerve	White Matter	Gray Matter
T1-weighted	Hyperintense	Hypointense	Hypointense	Intermediate	Brighter	Darker
T2-weighted	Less hyperintense	Hyperintense	Hypointense	Intermediate	Darker	Brighter
Short tau inversion recovery (STIR)	Hypointense	Hyperintense	Hypointense	Intermediate	Darker	Brighter
T1-postcontrast	Normal enhancement of vascular structures, abnormal enhancement at sites of blood-brain barrier disruption and hypervascularity (tumor, infection, inflammation, demyelination)					

Landmarks and orientation to spinal level

Imaging of the cervical spine (7 cervical vertebra) typically includes the occiput through the first thoracic vertebral levels; the thoracic spine (12 thoracic vertebra) includes the inferior cervical and superior lumbar levels; and the lumbosacral spine (5 lumbar vertebra) includes the inferior thoracic level through the mid sacrum. Remember that there are eight cervical spinal nerves and only seven vertebra: thus, each spinal nerve is named for the vertebra just below the interspace, e.g. the 5th cervical spinal nerve root lies between the 4th and 5th cervical vertebra. In contrast, the eighth cervical spinal nerve lies between C7 and T1 and all thoracic and lumbar spinal nerves are named for the vertebra directly above the interspace, e.g. the L4 spinal nerve lies in the foramina between L4 and L5.

The easiest means to get oriented when starting to interpret a new study is to use a sagittal series image and scroll to the midline, where the vertebral bodies can be clearly seen (Figure 1).

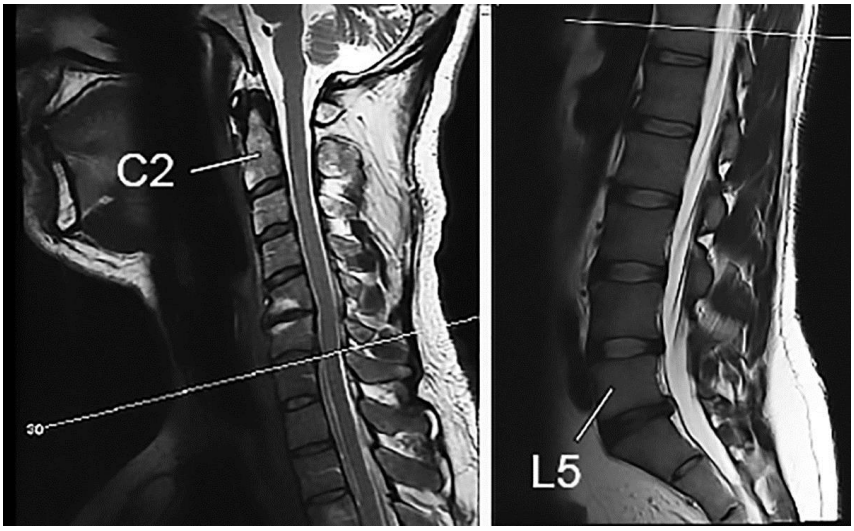

Figure 1. Identifying the cervical and lumbar vertebral level.

For the cervical spine, the characteristic appearance of the odontoid process of C2 is easily identified; all adjacent vertebra can be numbered by counting downward. For the thoracic spine, T1 and T12 are easily identified as the superior-most vertebra and inferior-most vertebra with an articulating rib adjacent to the vertebral body, respectively. The lumbar spinal level is determined by identifying the L5/S1 junction, where the inferior-most vertebral body (rectangular in appearance) lies just superior to the sacrum (trapezoidal in appearance). While there are numerous anatomic variations, including lumbarized sacral segments and additional vertebra in some individuals, naming the vertebral body by the MRI appearance, describing in your records how the vertebral level was named, and remaining consistent will help avoid errors when describing the vertebral level where abnormalities are to be tartgeted with treatment.

Vertebral alignment and height

The normal spine appears curved when viewed in the sagittal plane, with a cervical lordosis averaging 20 degrees, a thoracic kyphosis averaging 35 degrees, and a lumbar lordosis averaging 29 degrees.[1] Abnormal lateral deviation of the spine, or scoliosis, is defined as lateral deviation of more than 10 degrees. This is best seen on coronal images, where bowing to the left (levoscoliosis) or right (dextroscoliosis) can be accurately measured. The anterior and posterior surfaces of adjacent vertebral bodies should be in alignment. When one vertebral body is displaced relative to the adjacent vertebral body, the condition is termed spondylolisthesis (anterolisthesis, when the superior vertebra slips anterior relative to the inferior vertebra and retrolisthesis the opposite). The most common form of this disorder is degenerative, but in children and adolescents, spondylolysis, where fracture of the pars interaricularis (the bone that connects the lamina medially to the superior and inferior articular processes of the facet joints laterally) allows for slippage of one vertebra over another. Spondylolisthesis is graded by the degree of overlap of one vertebral body versus the other: grade 1, 0-25% displacement; grade 2, 26-50%; grade 3, 51-75%; and grade 4, 76-100%. Spondylolisthesis can lead to significant instability and compromise of the neural foramina and the central spinal canal and be associated with symptomatic compression of the spinal nerves or spinal cord. Pars interarticularis defects and other fractures and misalignments should be sought whenever spondylolisthesis is found.

The MRI appearance of progressive degeneration of the vertebral endplates (the bone facing the intervertebral discs was classified by Modic.[2] (Figure 2)

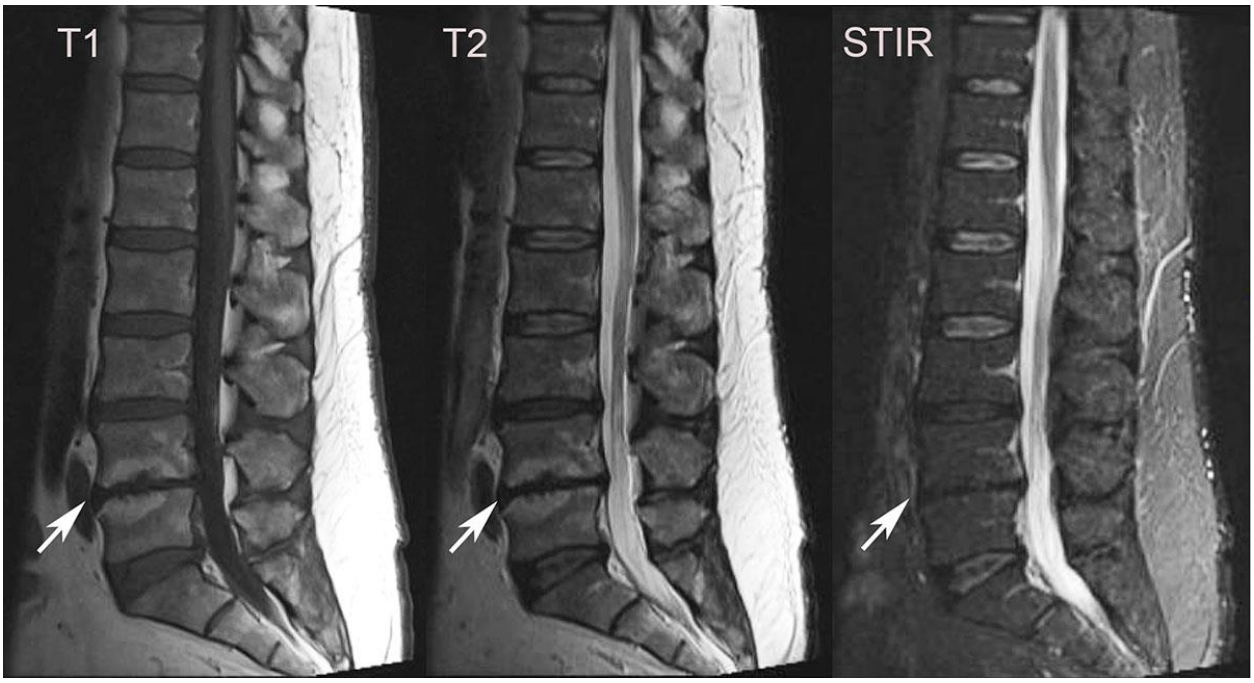

Figure 2. Type 2 Modic changes in the vertebral bodies adjacent to the L4/5 intervertebral disc. Type II changes are T1 and T2 hyperintense and correlate with replacement of bone marrow by fat. Suppression of the T2 hyperintensity on STIR sequence further confirms the presence of fat.

Type I Modic changes are T1 hypointense and T2 hyperintense and correlate with formation of granulation tissue subjacent to the endplates. Type II changes are T1 and T2 hyperintense and correlate with replacement of bone marrow by fat. Suppression of the T2 hyperintensity on STIR sequence further confirms the presence of fat. Type III change appear T1 and T2 hypointense and correlate with longstanding and chronic degeneration of the endplates. Other common degenerative changes seen on both CT and MRI are the formation of osteophytes and/or disc-osteophyte complexes. These bony overgrowths occur most commonly along the margins of the vertebral endplates and at the margins of the articular surfaces of the facet joints. As they enlarge, these bony deposits can narrow the dimensions of the spinal foramina and the central spinal canal and impinge on adjacent neural structures, causing pain and other characteristic neurologic symptoms of spinal and foraminal stenosis.

Vertebral height increases from the cervical level to the lumbar levels with average vertebral heights of 1.4 cm at cervical levels, 1.8 - 2.3 cm at thoracic levels, and 2.6 – 2.8 cm at lumbar levels. Loss of vertebral height is most often due to trauma and is often accompanied by conditions that weaken the vertebra, including osteoporosis and primary or metastatic tumors. Vertebral fractures are graded by the degree of loss of vertebral height[3] and the shape of the deformity.[4] The most common vertebral compression fracture is associated with loss of bone density and presents as a wedge-shaped deformity of the vertebral body, typically with isolated collapse of the anterior aspect of the vertebral body and preservation of the height of the posterior aspect. Hemangiomas are common abnormalities of the vertebral body and are well-circumscribed lesions containing fat and vascular tissue. They appear hyperintense on both T1- and T2-weighted sequences as well as the STIR sequence; because of their vascularity, contrast enhances hemangiomas. Schmorl's nodes (Figure 3) are also commonly seen in patients with degenerative disease of the spine are caused by a focal prolapse of disc material through the adjacent vertebral end plate. They produce what looks like a focal hole in the vertebral end plate and their signal characteristics are similar to disc material.

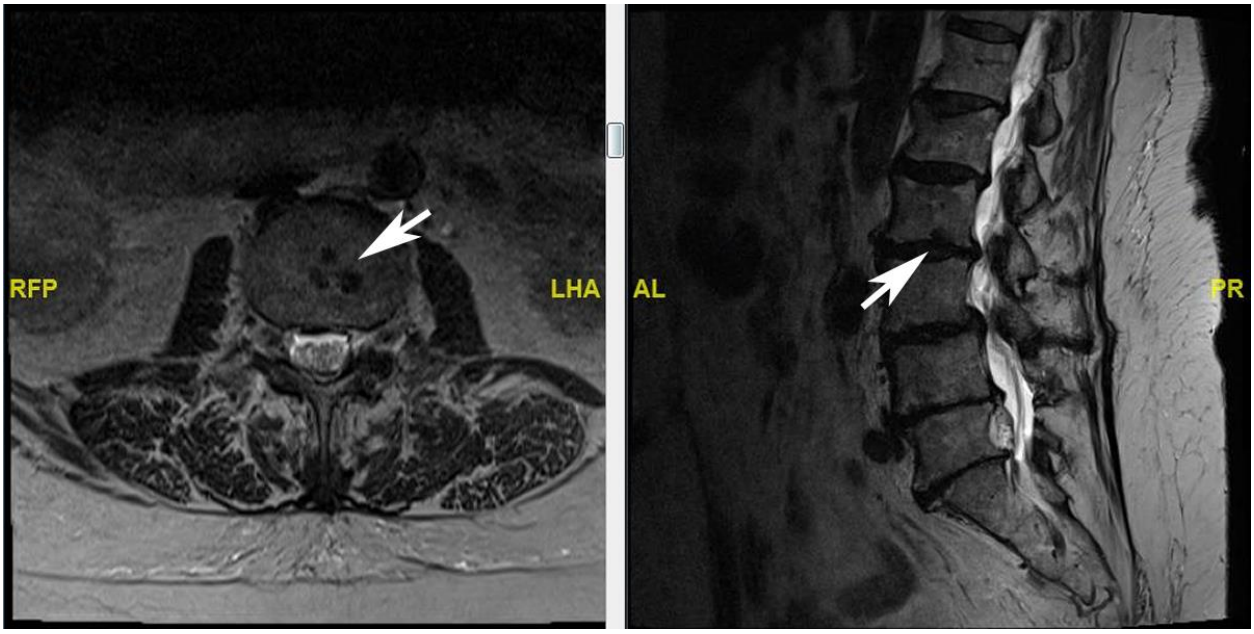

Figure 3. Schmorl's nodes are commonly seen in patients with degenerative disease of the spine are caused by a focal prolapse of disc material through the adjacent vertebral end plate.

Disc appearance and height

The intervertebral disc is comprised of the central nucleus pulposus surrounded by the outer annulus fibrosis. The nucleus polposus is comprised of glucosaminoglycan that is normally well hydrated and thus is hyperintense on T2-weighted images. The surrounding annulus fibrosis is less well hydrated and thus relatively hypointense on both T1- and T2-weighted sequences. As we, age the nucleus gradually loses hydration and the T2-weighted images reveal a loss of the hyperintense signal. The annulus also loses hydration and small fissures can appear within the annulus. These fissures can acutely worsen with activities like heavy lifting that place mechanical stress on the discs. With an increase in pressure within the central disc, material from the nucleus pulposus can suddenly produce a radial tear within the annulus. If the nuclear material stays within the confines of the annulus, a small track of T2-hyperintense material can often be seen extending radially from the nucleus toward the outer annulus, an annular tear. Disc material that extends beyond the limits of the annulus is termed disc herniation. Disc herniations are classified according to their shape and continuity with the central nucleus (Figure 4). A disc protrusion remains in continuity with the central nucleus and the base is longer than the portion that extends beyond the limits of the annulus fibrosis. A disc extrusion is present when the base is shorter than the portion that extends beyond the limits of the annulus fibrosis. An sequestered disc fragment is present when the disc fragment completely separates from the disc of origin. As degeneration progresses, the intervertebral discs progressively lose height, leading to a bulging of the redundant annulus. When disc bulges are oriented posterolaterally, they can impinge upon the spinal nerves in the lateral recess of the spinal canal and produce radicular pain; far lateral disc bulges and herniations may impinge on the spinal nerves within the intervertebral foramen.

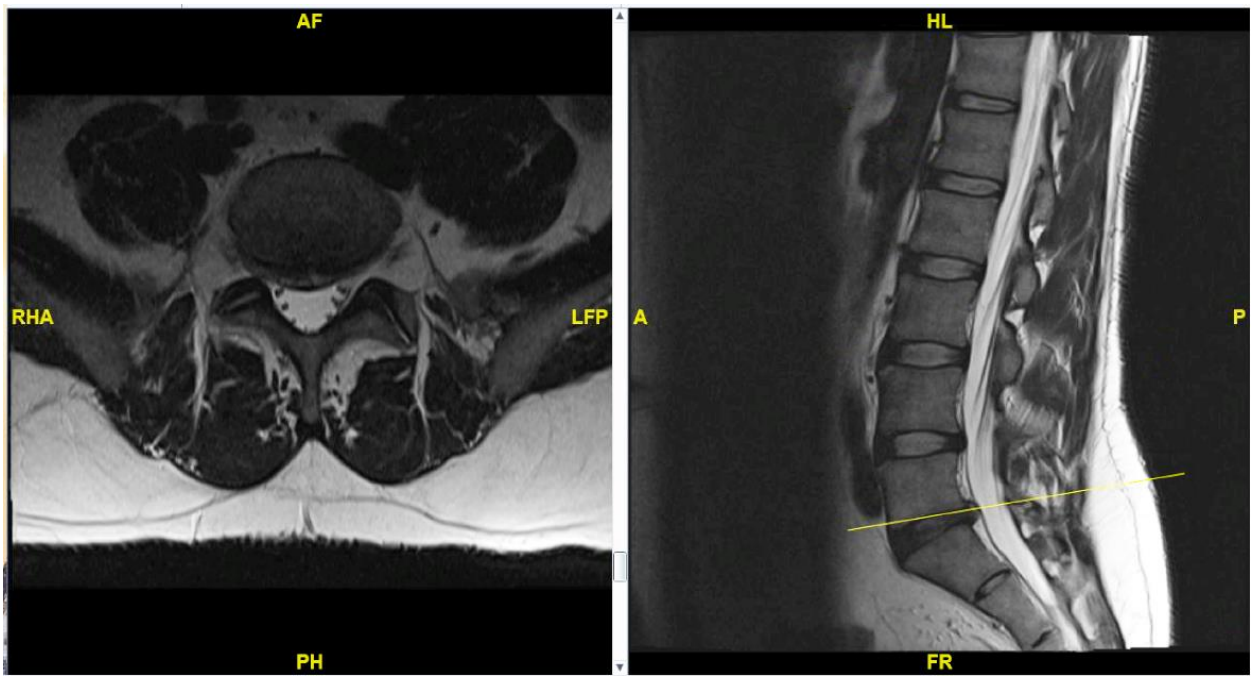

Figure 4. Axial and sagittal T2-weighted images demonstrating loss of disc height and hydration at L5/S1 with a right posterolateral broad-based disc bulge adjacent to the right S1 spinal nerve without nerve compression.

Ligaments

There are three predominant ligaments that provide structural support and flexibility to the spine. The anterior longitudinal ligament extends between the anterior surfaces of the vertebral bodies along the entire course of the spine. The posterior longitudinal ligament extends between the posterior surfaces of the vertebral bodies along the entire course of the spine and thus is located at the anterior most aspect of the spinal canal itself. The ligamentum flavum is just anterior to the paired spinal laminae along the posterior aspect of the spinal canal. Redindnacy and ossification of the ligaments can lead to facol neural impingement and/or narrowing of the central canal to such an extent that symtoms appear.

Spinal canal

The dimensions of the spinal canal can be altered by congenital abnormalities of degenerative changes of spinal structures described above (Figure 5). The anterior-posterior diameter of the spinal canal is fairly constant from cervical to lumbar regions, between 15 and 20 mm. Within the canal, the posterior longitudinal ligament is found anteriorly along the posterior aspect of the vertebral bodies, while the ligamentum flavum is located centrally along the posterior aspect of the spinal canal. Laterally, the canal is bounded on both sides by the medial aspect of the paired facet joints.More centrally, surrounding the thecal sac is a thin layer of epidural fat containing a rich network of epidural veins.

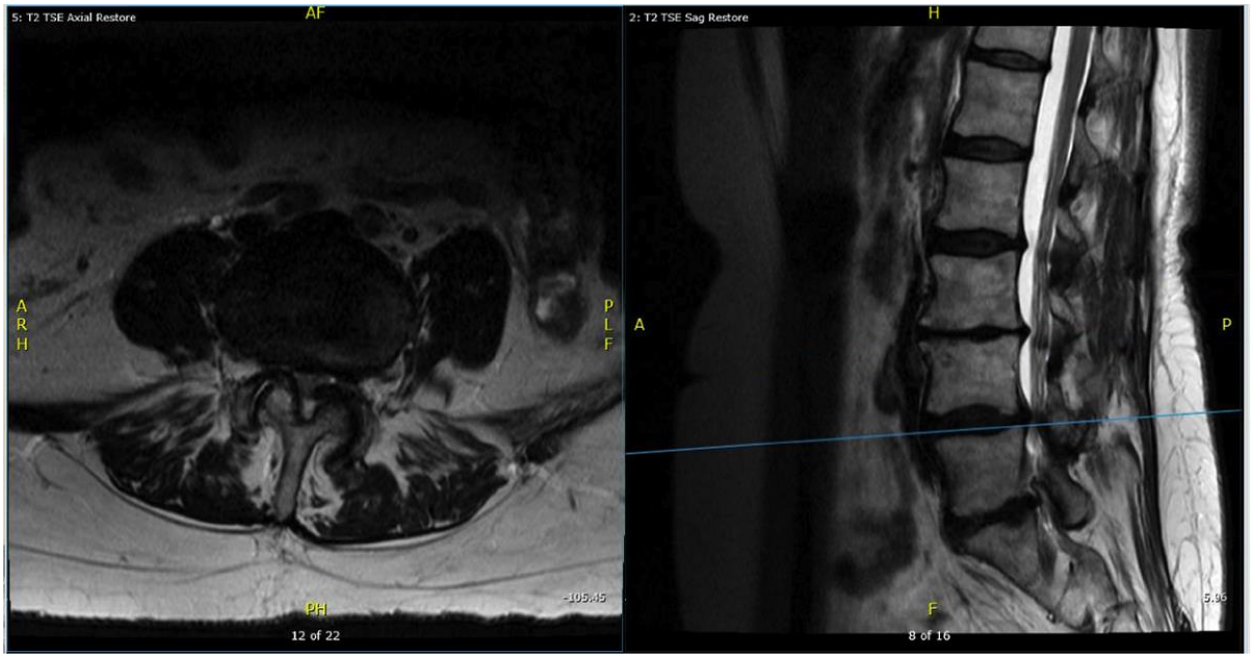

Figure 5. Axial and sagittal T2-weighted images demonstrating advanced degenerative changes, with loss of disc height and hydration at all levels and severe stenosis of the central spinal canal at the L4/5 level caused by grade 1 spondyolisthesis in conjunction with severe bilateral facet hypertrophy. Note the complete absence of CSF surrounding the cauda equine in the axial image.

Paraspinal soft tissues, cord position, blood supply

Advanced practitioners will gain additional familiarity with systematically assessing the paraspinal soft tissues for unexpected abnormalities, verifying the position of the spinal cord within the canal to detect abnormalities that cause cord displacement. Understanding the blood supply to the cord and the ramifications of this anatomy are also important in assessing the patient who has suspected vascular injury to the spinal cord. These topics are beyond the scope of this review. For an excellent review see the recent article by Klein.[5]

Putting it all together: using a stuctured approach to image interpretation

It is always best to localize spinal lesions clinically, based on history and physical examination. Image only the focused area that the signs and symptoms point toward. Table 2 lists the specific tasks that should be covered systematically during image interpretation.

Table 2. Systematic approach to limited interpretation of spinal imaging for the pain practitioner (modified from reference 5)*

Structure	Task
Vertebral alignment	Label and count vertebra, assess lordosis/kyphosis, look for scoliosis and spondylolisthesis
Vertebral height and signal	Assess for compression fractures, masses, and pathologic marrow replacement, inflammation
Disc height and signal	Assess for disc degeneration, bulging, herniation
Ligaments	Assess for non-linearity, tears, hypertrophy, or inflammation
Meninges	Assess for nerve root clumping or masses
Spinal canal and neural foramina	Assess for narrowing of the central spinal canal, lateral recesses of the spinal canal and neural foramina, spinal nerve compression, masses, or inflammation

*Complete interpretation should include assessment of the paraspinal soft tissues, cord position, blood supply.

Adopting a standardized routine for reviewing imaging studies will assure that all elements are assessed and that subtle findings do not go unnoticed. Start by displaying the imaging studies and sequences in a standardized layout and in a specific order. I prefer to begin with the sagittal T2-weighted series to the right of a 2-panel screen and the axial T2-weighted series to the left. By scrolling to the mid-sagittal plane, the vertebral bodies can be identified and numbered and a quick scan of the mid-sagittal image will reveal important information about vertebral alignment, vertebral height and signal and disc height and signal, ligaments and the anterior-posterior dimensions of the spinal canal in the midline. When the image in the mid-sagittal plane demonstrates that the vertebra are not all aligned in the midline (the mid-sagittal plane will pass through different planes from medial to more lateral in different vertebra), suggesting significant scoliosis, then a quick review of the coronal images allows precise assessment of the levels, direction and severity of the scoliosis. Returning to the T2-weighted series, a thorough review of the axial series from cephalad to caudad allows for detailed assessment of all elements of the vertebral bodies, discs, ligaments, meninges, spinal canal, foramina, and paraspinous tissues. When specific abnormalities are identified, assessing the T1-weighted, STIR, and T1-weighted post-contrast series allows for differentiation of fluid, fat, soft tissue and bone, to more fully characterize the nature and chronicity of the abnormalities identified as described in detail in the paragraphs above.

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Medical Errors: Unavoidable?

Ashish C Sinha, MD PhD DABA MBA Philadelphia, PA

Introduction

Many centuries ago, Hippocrates discussed the concept of medical errors and he may have coined the word *iatrogenesis*, from the Greek language for *originating from a physician.* In the mid-20th century NEJM published a review article on *Diseases of Medical Progress*, which eventually became a book with the phrase 'Iatrogenic Disease' in its title. Later in 1978, the Medical Insurance Feasibility Study, which was designed to quantify patient disabilities from health care management, was set up to try to identify potentially compensable medical injuries. This Study from forty years ago, from California estimated 4.65 injuries per 100 admissions. Future studies more than doubled this number, to 10 to 12%, with more than half of these being considered preventable.

Demographics

Globally, it is now estimated that medical errors affect one in 10 patients worldwide! A few years ago, the Common wealth fund revealed that more than a fifth (22%) of Americans reported that they or a family member had experienced a medical error of some kind.

The issue of medical errors, or human errors as they are sometimes referred to, and their devastating cost to both individuals and society was initially brought into the open in the 1999 publication from the Institute of Medicine's publication "To Err is Human" showing that health care is not as safe as it should be. The book used the examples of error rates with deadly outcomes in states of Colorado and New York, and by extrapolating this number to all US admissions, postulated that between 44,000 and 98,000 patients were dying in US hospitals due to medical errors every year! At those numbers, in 1999, deaths from medical errors exceeded deaths from breast cancer or motor vehicle accidents. As a corollary, in the same time frame the number of preventable injuries to patients exceeded a million.

In the UK, a 2000 study estimated the number of annual medical injuries at 850,000 at a cost of over £2 billion. In 2010, the Office of Inspector General for Health and Human Services said that bad hospital care contributed to the deaths of 180,000 patients in Medicare alone in a given year. Subsequently a study in the *Journal of Patient Safety* said that the numbers are much higher, by doing chart reviews and applying a method called 'Global Trigger Tool' which screens charts for infection injury or error. In a study covering over 4000 patients adverse events happened in over 20% of the time and lethal events may have been in the 1.4% range. By extrapolating that to the 34 million US hospital admissions in 2007, the deadly number rises to over 200,000. The global trigger tool though efficient at identifying errors of commission, misses the errors of omission which could easily double the number of

preventable deaths and now we could be staring at nearly half a million deadly medical errors! In 2015, per the American Hospital Association Statistics there were over 35 million admissions in the 5564 registered US hospitals. The average length of stay is almost 5 days, giving a potential **175 million patient days** for a medical error to occur!

In terms of harm, medication errors are some of the most common medical mistakes. Wrong drug, wrong dose, wrong time, wrong route, and or the wrong patient can all have a significant and potentially deadly impact on outcomes. As one would predict, the location within the hospital for most errors to occur are areas of the sickest patients, and stressful environment; namely the ER, the ICU and the ORs. Additionally high risk procedures like surgery and high risk specialties, *like anesthesia*, are responsible for most avoidable adverse events. As expected complex procedures entail more risk, but also additionally, when an error occurs, the outcomes are worse. Another study estimated that the most common medical mistakes harmed at least 1.5 million people each year. In terms of considering just drug related injuries, approximately 400,000 injuries occur in hospitals, and an additional 800,000 in long term care facilities; more than half a million such injuries occurred in Medicare recipients in outpatient clinics. The problem is pervasive, serious and does not get enough exposure due to a very human tendency to either deny or deflect the cause of the end result, whether it is minor harm, major harm or death. Therefore it is hard to get a true measure of medical errors. Negligence may account for 1% errors in all hospital admissions.

Causes of Errors

Healthcare is complex, sick patients, sometimes critically, are treated in acute or intensive care with powerful technologies and potent drugs, by humans who may be tired, inadequately trained, or inappropriately supervised. The component of fatigue in the error landscape is starting to be addressed after being identified. Statistics like being awake for 24 hours increases the rate of medical errors two or three fold, including those resulting in injury and death! Post a 24 hour shift, the rate of car accidents almost doubles with a nearly fivefold increases in near misses.

Health care systems are not efficient or as safe as they could be. This includes ergonomics like poor lighting which can contribute, for example to identifying a drug syringe incorrectly, small spaces where it would be hard to get help to assist in the care of a critical patient or loud music drowning out a machine alarm. These are system issues, not indicating dishonest work but the medical provider being handcuffed by the limitations of the system.

Poor communication is involved front and center in error issues. In many errors clear and early communication would have prevented the error from happening or mitigated the adverse effect of the event. The time out performed (or as it should be performed) routinely in ORs across the world does a lot to break down the initial barrier of silence that may allow the error to occur. If you ‘see something say something’ should be replaced with ‘if you think something ask something’. The author firmly believes that there are no stupid questions, only stupid answers!

Clinical care is a team ‘sport’ with joint and several liability and responsibilities. Legally we are all exposed in the operating room or anywhere where clinical care is being provided to a patient. This is an

instance of where everyone assumes, erroneously sometimes, that the performer of the action knows what they are doing or 'it must be OK' if Dr Bigwig is doing it. Wrong sided surgeries are a good example of this phenomenon. In recent times a surgeon misidentified the kidney to be removed in a patient and on being questioned by the medical student in the room, told the student to be quiet. The consequence of this was a follow up nephrectomy (on the diseased side), dialysis and eventually death from complications. This event resulted in a deadly error, in this case involuntary manslaughter, being performed when there were many opportunities to have prevented it. Another incident resulted in the enucleation of the wrong eye in a 5 year old girl, not the eye with the retinoblastoma! Wrong sided surgeries can be devastating and deadly. Multiple safety stops can eliminate this one cause of morbidity and mortality. Ineffective team communication, especially in the operation room (OR), is a major root cause of these errors.

Variations in training can affect error rates, the *July effect* (or *July syndrome)* is a good example of this, which shows that more medical and medication errors are made in July when new members join the training team.

Handling Errors

The occurrence of errors in medicine are a given. The rate of errors needs to be the least possible for any error and close to zero, if not zero, in avoidable errors. What should we do when we are the cause of an error which occurs? This is a personal and professional challenge for every clinician. How one reacts, the first time one makes a significant error of omission or commission, judgment or execution might impact the future handling of all errors. Explaining to colleagues, admitting to patients, fixing the problem as best as possible, making financial compensation if indicated and forgiving oneself are all part of dealing with this inevitability for all clinicians. It is important to the patient to know what happened, why the error happened, how will the effects of the error be mitigated, and how will this be prevented in the future. Unfortunately, at least in the past, the patient and family ran into a wall of silence and denial. With honesty, healing can begin for both victims, since the medical provider is also a victim of the error in this situation. According to Levinson's study from University of Toronto, when discussing a medical error, surgeons may use the phrase 'error or mistake' only half the time and an apology even less than half the time!

Disclosure

Patient disclosure is important in the medical error process. The current standard of practice at many hospitals is to disclose errors to patients when they occur. In the past, it was a common fear that disclosure to the patient would incite a malpractice lawsuit. Many physicians would not explain that an error had taken place, causing a lack of trust toward the healthcare community.

In 2007, AHRQ reported that 34 had states passed legislation that precludes any information from a physician's apology for a medical error from being used in malpractice court (even a full admission of fault). This would encourage medical practitioners to acknowledge and explain mistakes to patients, thereby building trust and an open line of communication.

The American Medical Association's Council on Ethical and Judicial Affairs states in its ethics code: "Situations occasionally occur in which a patient suffers significant medical complications that may have resulted from the physician's mistake or judgment. In these situations, the physician is ethically required to inform the patient of all facts necessary to ensure understanding of what has occurred. Concern regarding legal liability which might result following truthful disclosure should not affect the physician's honesty with a patient."

And from the American College of Physicians Ethics Manual: “In addition, physicians should disclose to patients information about procedural or judgment errors made in the course of care if such information is material to the patient's well-being. Errors do not necessarily constitute improper, negligent, or unethical behavior, but failure to disclose them may.” However, "there appears to be a gap between physicians' attitudes and practices regarding error disclosure. Willingness to disclose errors was associated with higher training level and a variety of patient-centered attitudes, and it was not lessened by previous exposure to malpractice litigation".

Consequently, in the United States, many states have enacted laws excluding expressions of sympathy after accidents as proof of liability. However, "excluding from admissibility in court proceedings apologetic expressions of sympathy but not fault-admitting apologies after accidents"

Interestingly disclosure of errors has been shown to actually reduce malpractice payments. Patients and their family members find vindication of what their feelings of anger and helplessness and might help them forgive and maybe even accept a bad outcome as the result of an error, maybe negligence but not intentional harm.

Mickan described six characteristics, which are self-explanatory, of an effective team involving:

1. Purpose,
2. Goals,
3. Leadership,
4. Communication,
5. Cohesion, &
6. Mutual respect.

Incorporating these qualities into medical communities can minimize errors and improve patient safety

Following the recommendations of the Safe surgery saves lives, the WHO program, is an easy step in starting the process of decreasing the rate of an unacceptable event. After all even if medical errors are unavoidable, by incorporating the points mentioned in these paragraphs, we can get from an unacceptable rate of an unacceptable event towards an acceptable rate of an unacceptable event.

Further Reading

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Turning Off The Gas: The Aging Anesthesiologist

Jonathan D. Katz, M.D. **New Haven, CT**

Physicians are useless after age 60 and as such should retire to a college for a year and then be euthanized with chloroform. [a]

The learning objectives of this lecture are to:
1) Identify some commonly observed physiologic changes associated with aging.
2) Discuss how normal aging might impact the late- career anesthesiologist.
3) Understand the pros and cons of mandatory cognitive screening for senior anesthesiologists.
4) Examine the impact of the aging population of anesthesiologists on the anesthesiology workforce.
5) Discuss some arrangements between senior anesthesiologists and their associates that can benefit the individual anesthesiologist, his/her group, and their patients

INTRODUCTION: The population of the United States is aging. In 1990, less than 13% of the American population, some 31 million individuals, were older than 65 years of age.[b] By 2016, those age 65 years and older had expanded to greater than 48 million—close to 15% of the U.S. total.[c]
Aging anesthesiologists has progressed in a parallel fashion. In 1990, the largest age group of active members of the American Society of Anesthesiologists (ASA) was between 35 and 44-years of age. [d] They accounted for close to 33% of the overall membership. As of 2017, the 55 to 64 age group has become most numerous (29.1%). [e] Anesthesiologists older than 65 years now account for 8% of those active.
Aging among anesthesiologists has implications for the nature of the individual anesthesiologist's practice and the overall anesthesiology workforce. In the following discussion, we will consider some of the common physiological changes associated with aging and how they might affect the practicing anesthesiologist, his or her colleagues, and their patients.

THEORIES OF AGING: All living creatures, including anesthesiologists, age. Aging in humans is a multidimensional process involving physical, psychological, spiritual, and social changes. Some abilities and skills are enhanced, such as experience and wisdom, and others decline, such as processing speed and various aspects of memory.
Aging involves a wide variety of sequential and progressive physiological changes that result in decline of the efficient functioning of many biologic processes. Ultimately, increased vulnerability to injury, illness, and death ensues.
There are several different types of aging. Chronological aging, which refers to how many years have passed since an individual's birth, is arguably the most straightforward concept. But "biological aging"—an organism's physical and psychological state as it ages—is more relevant to considerations concerning the professional life of an anesthesiologist.
There are a variety of theories as to exactly why and how aging occurs. In general, all the theories fall into two overlapping categories. The *programmed theories* hold that aging follows a biological timetable that encodes a sequential switching on and off of certain genes, and is a continuation of the processes that regulate growth and development that begin at conception. One popular model suggests that telomeres, the DNA caps on the ends of chromosomes, play a pivotal role by regulating and ultimately impeding cell division. The *damage* or *error theories* emphasize environmental assaults to an organism that gradually cause wear and tear and cellular damage.

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[a] Taken from a retirement address at Johns Hopkins University by Sir William Osler (1905). Dr Osler subsequently enjoyed an additional 10 highly productive years as Regius Professor at Oxford University. Cushing H. The Life of Sir William Osler. Oxford: Clarendon Press; 1925
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[d] American Society of Anesthesiologists, personal communication, (2005)
[e] American Society of Anesthesiologists, personal communication, (2016)

Whatever the underlying process, aging begins at conception and continues through all stages of life. It is characterized by degenerative changes in the structure and functional reserve of cells and tissues. The accumulation of these changes over time results in the ubiquitous organ system changes and the aging phenotype. The end stage of the process results in death of the organism.

PHYSICAL CHANGES ASSOCIATED WITH AGING: The aging process occurs throughout all stages of life. Cellular aging is associated with degenerative changes in the structure and functional reserve of tissues resulting in the gradual deterioration of the organism's organ systems. The accumulation over time of these changes results in the easily recognizable aging phenotype.

Aging does not occur homogeneously. There are large intra- and inter- species differences in how aging progresses. Even within any one individual, different organ systems age at different rates and in dissimilar manners. One common denominator is a decrease in physiologic reserves. Aging organ systems work at maximum capacity simply to maintain homeostasis. They are unable to recruit the additional responses necessary to compensate for a stressful challenge, such as infection. This state, called "homeostenosis", leads to increased vulnerability to disease, a common observation seen among aging organisms.

Several age related physiologic changes which appear in all individuals at varying times and in various degrees of intensity carry the potential of directly impacting an anesthesiologist's practice:

1) There is a generalized decrease in muscle mass with accompanying loss of strength, fine motor skills and stamina. Older workers are particularly sensitive to the demands imposed by fatigue and have a decreased tolerance to shift work cycles and a greater tendency to late night errors. [1] It is not surprising that extended work hours and night call are among the most stressful aspects of anesthetic practice for older anesthesiologists and the most important reasons for retirement. [2]

2) Presbycusis, (hearing loss in the high frequency range) begins in early adulthood and progressively causes deterioration of hearing. Anesthesiologists are particularly vulnerable to age related hearing loss, especially in the higher ranges where many of the alerts and alarms of anesthetic equipment occur.[3] One or more common anesthesia alarms are below the threshold of detectability in 39% of anesthesiologists age 65 years and older.[3] The problem is exacerbated by the high ambient noise commonly experienced in operating rooms that can exceed that found in the hospital's cafeteria or boiler room. [4]

3) Visual impairments resulting from cataracts and other age related ailments can contribute to a reduction of visual acuity. This can be especially problematic when an older physician is attempting to complete visually complex clinical tasks.

4) There is an accelerated death of neurons, as well as a decrease in the size of neurons and the number of connections between them. This results in a measurable decrease in brain weight and volume as individuals age. The loss of gray matter is greatest in the frontal and temporal lobes. There are also significant changes in the volume and structure of white matter. Also observed are reductions in the total length of the brain's myelinated axons. These organic losses may be countered by other changes such as the development of redundant neural pathways and synaptic plasticity. Neurotransmitters and receptors also change with age- with some decreasing and others increasing.

COGNITIVE CHANGES ASSOCIATED WITH AGING: Cognitive changes frequently associated with normal aging can impact the practicing anesthesiologist. Cognitive changes are often described in the context of disturbances involving crystalized and fluid intelligence. Crystallized intelligence refers to skills and knowledge that accumulates over a lifetime of experience, such as language and general knowledge. This type of intelligence is usually preserved as individuals undergo normal aging. Fluid intelligence, such as processing speed and many memory functions, describes how adept an individual is at problem solving and reasoning when encountering a unique situation. Fluid intelligence begins to decline after the third decade of life.

Cognitive ability can be grouped into 6 specific categories: memory, processing speed, attention, language, visuospatial abilities, and executive functioning/reasoning. For many aging individuals memory loss is the most obvious and troubling of the changes. On average, a deterioration is seen among older individuals on tasks that require recollection of specific facts and events (explicit memory). On the other hand, implicit memory, that which is outside of one's awareness (such as riding a bike, or remembering the words to "Happy Birthday") tends to be preserved throughout life.

Processing speed, which is the speed at which cognitive activities are translated into motor responses, begins to decline during the third decade of life and progresses throughout the remaining lifetime. The slowing of processing speed can adversely affect performance of other neuropsychological tasks.

Attention deficits, especially those required for selective or divided attention tasks, tends to decline as individuals age. This can be particularly troubling in a noisy, dynamic, emotionally charged environment such as an operating room.

Other commonly observed cognitive changes that are particularly significant to anesthetic practice include: difficulties with learning; deterioration in creative thinking and problem solving abilities; slowing of on the spot reasoning, intellectual quickness and reaction time; decreased ability to form quick and effective decisions; and reduced performance on stressful and complex tasks.

In addition to normal cognitive changes, older individuals are more vulnerable to the many etiologic sources of dementia. Many of the diseases that are more frequently seen among older individuals, such as diabetes, stroke, and cardiovascular disease can further exacerbate routine age related loss of cognitive function. As many as 15% of those over age 65 have some degree of cognitive impairment.[5] In many cases, memory and language dysfunction are among the most prominent features.

It is important to note that many important aspects of psychology and cognition are frequently spared during normal aging. For example, optimism, resilience, compassion, long term memory, judgment, and wisdom all may be preserved and even enhanced with age. The administration of a safe and successful anesthetic relies on a vast array of clinical skills, including technical agility, experience, and judgment. These preserved attributes serve to augment retained clinical skills and can provide an advantage to an older anesthesiologist.

HOW NORMAL AGING MIGHT IMPACT THE PRACTICE OF ANESTHESIOLOGY: Each of the age-associated changes described above has the potential to impact the practice of anesthesiology. [6] For example, decreased visual acuity can make it more difficult to read drug labels or monitor displays in the varying ambient light conditions found in operating rooms. Musculoskeletal disease can hinder an older anesthesiologist's ability to run up several flights of stairs to attend to a non-operating room emergency. Hearing loss can interfere with the aging anesthesiologist's ability to hear vital conversations and alarms amid the cacophony commonly occurring in a modern operating room.

Cognitive impairment poses the most threatening challenge to safe anesthetic practice and has received the most attention. The correlation between normal cognitive aging and an enhanced risk of motor vehicle accidents provides some insight into the manner in which cognitive impairment might adversely affect safe anesthetic practice. [7] Several studies have demonstrated an age-dependent decline in the knowledge base and performance on certification examinations among older physicians [8] However, there is considerable variability, such that older physicians tend to perform less well **on average,** but many score at the same or at a higher level than their younger colleagues. As observed by Eva, "one of the more robust findings in ageing research is that the variability across the scores individuals receive tends to increase with age." [8]

A similar pattern emerges from those studies that looked at the relationship between physicians' age and clinical outcomes- especially among preceduralists performing complex interventions. Several reports have identified increased complication rates in certain high risk procedures performed by older surgeons. For example a study of carotid endarterectomy found that mortality increased as a function of surgeons' age. [9] A different study that examined outcomes of inguinal hernia surgery found that the risk of recurrence after laparoscopic repair was 1.72 times higher for surgeons older than 45 years than their younger colleagues. [10] The authors of this study suggested that the cognitive changes associated with aging rendered the older surgeons less able to learn and perform complex new procedures -in this case laparoscopic surgery. And in a meta-analysis of physicians' performance on a variety of quality measurements, 73% of the studies demonstrated a negative association between age and length of time in practice and evidence of good performance. [11] Most of the studies demonstrated a global decline in all of the measures. Participation in traditional continuing medical education activities and recertification did not affect the findings in this meta- analysis.

Not all studies have identified physicians' age as an independent risk factor for unfavorable procedural outcomes. Experience can play a salutary role in overcoming some of the deficiencies that might occur due to a decreased fund of current scientific knowledge. A study of operative mortality in a select group of high risk procedures reported that surgeons' age was not an important predictor of adverse outcomes in 5 of the 8 procedures studied. [12] Even in those procedures where older surgeons did have a higher mortality rate, the effect of age was largely restricted to surgeons with low procedure volumes.

Comparable data are sparse for anesthesiologists. In one study that employed a simulator to test the ability of an operator to insert an emergency percutaneous cricothyroidotomy, age and years from residency were predictors of poor performance as measured by procedural time, checklist scores, and global rating scores. [13] Another study which was conducted among Canadian anesthesiologists demonstrated a 50% greater risk of being found responsible for

litigation among anesthesiologists older than 65 years as compared with anesthesiologists younger than age 51.[14] In addition, the severity of injury was 2 fold greater among older anesthesiologists.

On the other hand, an abstract presented at the ASA Annual meeting in 2015 failed to show any differences in clinical outcomes when comparing cases conducted by older (>age 54) vs younger anesthesiologists. [f] The authors did observe a significant difference in practice patterns in which older anesthesiologists were less likely to be involved in complex surgical procedures.

POLICIES TO ASSESS "FITNESS FOR DUTY" AMONG AGING ANESTHESIOLOGISTS: Optimally physicians would recognize their own limitations and restrict their practice before any patient harm occurs. Unfortunately, impaired physicians are often the last to know. Physicians tend to be poor self- analysts and routinely fail to identify or report their own failing competence. In fact, physicians who are the least competent are also the least able to accurately judge their own skills and often give the appearance of being the most self- confident. [15] Physicians are also rarely able or willing to report failing competence among their own colleagues. Although most physicians acknowledge the duty to report incompetent or impaired colleagues, only 2/3 have taken appropriate action when faced with the situation. [16]

In the absence of adequate self- policing as a safeguard for public safety, many health care organizations, medical boards, certifying bodies and medical societies, such as the American Medical Association and the American College of Surgeons, have issued statements and are developing their own policies and procedures. These span the spectrum from benign neglect to imposition of a mandatory retirement age. Most are somewhere in the middle and act by requiring a physical, cognitive and psychological assessment, as well as focused case reviews on a regular basis once the clinician has achieved a predetermined age (most commonly 65 or 70 years). The ASA is relatively silent on the subject stating only that, "The practice of quality anesthesia care requires that anesthesiologists maintain their physical and mental health and special sensory capabilities." [g]

There are differences of opinion regarding the advisability of mandatory screening of all physicians based solely upon age. Advocates point to the fiduciary responsibility of organized medicine to police itself. Opponents cite the lack of validation of the frequently employed screening tools when applied to the varying demands imposed by practitioners in different specialties.

To be equitable, any comprehensive evaluation must be specific to the clinician's specialty and desired privileges. Done properly, these policies will avoid discrimination or imposition of unnecessary restrictions on older physicians. Optimally, these policies will serve the dual function of identifying impaired physicians and encouraging those with no impairment to practice longer.

LEGAL CONSIDERATIONS: Many industries in which public safety is an issue impose age –related work restrictions. For example, commercial airline pilots must undergo regular health screenings starting at age 40 and must retire at age 65 (increased from age 60 in 2007). The mandatory retirement age for air traffic controllers is age 55years and for FBI agents age 57. In contrast, there are no laws or regulations in the United States that mandate health screening or retirement age for health care providers (or Presidents of the United States).

The practice of medicine is a privilege and is accompanied by many responsibilities, including the obligation to remain physically, mentally and emotionally competent in one's profession. Historically, neither licensure nor hospital privileges have been specifically limited by the chronologic age of the practitioner. However, most state laws and hospital bylaws do require that a physician and/ or their colleagues report when there is substantial suspicion that professional skills may be compromised by any potential source of impairment, including age. Several federal laws, including the Age Discrimination in Employment Act of 1967 [h] and the Americans with Disabilities Act of 1990 [i] protect any worker from discrimination in employment due to age alone and outlaw compulsory retirement based solely upon age. Title II of the Americans with Disabilities Act pertains specifically to medical licensure and prohibits state and local governments from excluding qualified individuals from any government program, such as medical licensure or renewal.

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[f] Liau A. Outcomes and Practice Patterns of Older Anesthesiologists. Available at: http://www.asaabstracts.com/strands/asaabstracts/abstract.htm?year=2015&index=14&absnum=4523. Accessed 5/1/2017

[g] American Society of Anesthesiologists. Guidelines for the ethical practice of anesthesiology. Available at https://www.asahq.org. . Accessed 5/1/2017

[h] 29 U.S.C. § 621 through 29 U.S.C. § 634

[i] 42 U.S.C. §§ 12101 et seq.

However, there are important exceptions to protections afforded by these laws. A significant limitation to their applicability is whether the worker is an "employee" with a written agreement with their employer. An anesthesiologist who is a contracting agent with a health care institution might not be eligible for protection according to that requirement. Also important is the condition that any individual who poses a direct threat to the health and safety of others is not considered a "qualified person" under the Americans with Disabilities Act. A case recently decided by the U.S. Court of Appeals for the Fifth Circuit (EEOC v. Exxon Mobil Corp), affirmed Exxon's right to consider age as a "bona fide occupational qualification," and has wide ranging implications for those considering such actions for other workers in safety sensitive areas such as anesthesiology.[j]

EMPLOYMENT ARRANGEMENTS FOR LATE CAREER ANESTHESIOLOGISTS: As stated in the introduction, the specialty of anesthesiology is aging. Currently, close to 30% of ASA members fall into the 55 to 64 year old age group. Those older than 65 years, account for an additional 8% of the total workforce.

The aging of the workforce accompanied by a predicted shortage of anesthesiologists has added to the imperative to develop arrangements to enable competent senior clinicians to continue working. Several factors play a role in plans to continue to employ senior associates. The size and business structure of a group and the collective philosophy of its members are major considerations. Polices for distributing call and vacation, dividing income, providing benefits and governing the group all are important factors. Because administrative costs and malpractice premiums are associated with each employee whether they are full or part time, the assignment of overhead expenses can be particularly problematic.

"Winding down" employment arrangements fall into 3 general categories:1) a shared position where 2 or 3 anesthesiologists agree to carry all of the clinical, administrative, and financial responsibilities of one partner; 2) a part time position in which 1 individual continues to perform all of the functions of a full time clinician but at a reduced rate- for example 2/3 call, 2/3 clinical time, etc.; 3) a part time position that completely eliminates some aspects of practice (for example night call) and limits exposure to the most complex procedures and other stressful elements of practice. Additional details on how these arrangements might work can be found in a review by Baxter.[17] The most challenging aspect of any of these arrangements the value these tradeoffs, which is specific to each situation and can only be made on a practice by practice basis.

One size does not fit all regarding flexible work schedules. Each group of anesthesiologists must develop a program specific to its unique situation. Those that work best usually address the following considerations: (1) assurance that any agreement conforms to applicable law; (2) a prerequisite that the senior partner has achieved a minimum combination of chronological age and years of service; (3) a clear agreement on the parameters of the part-time position, including responsibilities and limitations; (4) a detailed description of the total compensation package, including benefits; (5) a minimum work commitment to receive benefits; (6) an understanding of residual (if any) shareholder status and voting rights; (7) a declaration of plans to fully retire within a defined period; (8) a clear reinstatement policy; and (9) fairness for all—the plan must be available to other partners at a future time.

RETIREMENT: As previously discussed, there are no mandated retirement ages for physicians in the U.S.A. The decision to retire usually remains solely at the discretion of the individual anesthesiologist. Age is inevitably one of the leading factors in decisions concerning retirement. The median age of retirement for anesthesiologists as of 2012 was approximately 64 years. [2] Commonly cited reasons for retirement among older anesthesiologists include on-call responsibilities, financial considerations, lack of professional satisfaction, health concerns, and changes in governmental policies and the health care business climate. On the other hand, those older anesthesiologists who decide to postpone retirement cite career satisfaction, financial obligations, and the need to maintain health insurance for family members as the primary reason to remain in the workforce.

MORTALITY AMONG ANESTHESIOLOGISTS: As observed by the great Hank Williams Sr. "I'll Never Get Out of This World Alive"[k]. Death is an expected consequence of normal aging. There is a wide range of lifespans both within and between species and populations. American life expectancies have increased substantially in recent years. A male who is age 65 in 2016 can expect to live until age 84.3. [l] A woman who is age 65 can expect to live until age 86.6. About 25% of 65-year olds today will live past age 90.

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[j] EEOC v. Exxon Mobil Corp. Available at: http://www.ca5.uscourts.gov/opinions%5Cunpub%5C13/13-10164.0.pdf Accessed 5/3/2017

[k] Williams, Hank. Song Lyrics from " I'll Never Get Out of This World Alive " Available at www.youtube.com/watch?v=w7FQeFOBtBk Accessed 5/1/2017

[l] U.S. Social Security Agency. Available at http://www.ssa.gov/planners/lifeexpectancy.html Accessed 5/2/2017 Accessed 5/29/2016

Anesthesiologists are also living longer. Early reports expressed concern that the stressful nature of the job and the consequence of excessive exposure to potentially toxic substances such as anesthetic gases and radiation resulted in premature deaths among anesthesiologists. A more recent study has challenged that assumption and concluded that the age adjusted mortality rate among anesthesiologists is not different than among other physicians. [18] The commonest cause of death among anesthesiologists has also changed over the past 50 years. Early reports cited a concern about an excess risk of cancer related mortality. More recent reports cite a disproportionate number of drug related deaths and suicide. [19]

CONCLUSION: Aging is a universal process that affects every clinician. Aspects of aging impart both advantages and disadvantages to the late- career anesthesiologist. A working arrangement can frequently be forged that benefits the anesthesiologist, the group, and their patients.

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ANESTHESIOLOGY 2017
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Clinical Hemodynamics: Assessment and Management

Jeffery S. Vender, M.D., MCCM, FCCP, MBA **Chicago, Illinois**

Anesthesiologists typically receive direct feedback when they deliver a fluid bolus to a surgical patient which, results in an increase in blood pressure and/or urine output. This process is interpreted as "fluid responsiveness" or an improved cardiac output (via a boost in preload/stroke volume). We ultimately hope this intervention leads to an improvement in end organ perfusion and subsequent favorable clinical outcomes. Realistically, this often times takes a leap of faith that in order to become a reality requires a far more advanced level of knowledge, applied science and appropriate therapeutic intervention.

Fundamental knowledge of hemodynamics is required in order to appropriately interpret physiologic responses in different clinical settings. Cardiac output (CO=SV x HR) is predicated on the heart's function and venous return function (i.e. preload). Well over 100 years ago, Frank and Starling demonstrated that an increase in end diastolic volume typically resulted in a greater cardiac force that produced an increase in cardiac output. The now famous Frank-Starling curve taught in basic physiology courses in medical school infers that afterload, heart rate and contractility are all constant (CO=MAP-RAP/ SVR). When heart rate or contractility increase or afterload decreases, cardiac output increases for any given preload (a leftward shift of the curve). However, after some point (plateau), a further increase in preload (end diastolic volume) will not result in further improvement in cardiac output. This maneuver will likely result in ventricular overdistension, overfilling and a reduction in end organ perfusion. The elegance of the Frank-Starling theory is echoed by "what comes in must come out."

The other vital component to cardiac output is the venous return (VR) function. Venous return is predicated on the elastic recoil of venous capacitance vessels. The mean circulatory pressure (Pms) minus the right atrial pressure divided by venous resistance equals venous return (VR=Pms-RAP/RVR). The heart controls its blood return by lowering right atrial pressure. An increase in stressed volume (volume stretching veins), results in a shift of the return function curve to the right. Venous resistance can also alter the return curve, where an increase in venous resistance leads to a decrease in venous return for a given right atrial pressure. Lastly, venous capacitance (the total venous volume for total pressure) is another component that restricts the circulatory system response. Veins have a small potential for contraction and when this threshold is reached, the so called, "unstressed volume" can no longer be utilized for improved cardiac output. This area is well discussed in a recent article by Gelman.

Plotting both the cardiac function and venous return function curves on the same graph allow for the clear depiction of the working relationship between these two important components. Physiologic and pathophysiologic states (shock) can be examined utilizing some of these premises. For instance, giving a fluid bolus to a hypovolemic shock patient will likely improve the associated cardiac output. However, giving fluid bolus to a patient who is past the plateau portion of the Frank-Starling curve could result in fluid overload and a worsened cardiopulmonary status. We will discuss the definition and pathophyisiologic explanations of shock (hypovolemic, cardiogenic, distributive and obstructive) in this talk.

Clinicians may use Goal-Directed Therapy (GDT) to address patients in shock like states (or with abnormalities in the cardiac function/return function relationship). Too often we have relied on monitoring and measurements (assessment) to alter outcome when it is actually the application of a therapeutic intervention (management) based on the information that alters outcome. Practitioners, who use goal directed therapy should recognize the following factors that most commonly will determine outcome: outcome: *appropriateness of care* (i.e interpreting data correctly and formulating the appropriate treatments), *timeliness* of care, and *responsiveness* (appropriate population targeted) to that care. **These axioms are vital to any clinician's success with goal directed therapy.**

Most GDT studies demonstrate improved clinical outcomes when appropriate physiologic end points are coupled with appropriate therapeutic measures, in a higher risk population, and *before end organ damage* occurs. The most difficult conundrum to address is which physiologic end points to use and how to accurately derive them. Endpoints of resuscitation can be divided into two categories; upstream and downstream. Upstream endpoints may include: hemodynamic (preload (CVP, PAOP, PPV)), contractility (SV), afterload (MAP, SVR)) and global oxygen delivery

parameters (arterial oxygen saturation and oxygen carrying capacity). Downstream metabolic endpoints may include: lactate, SVO2, pH, base deficit, tissue oxygenation, inflammatory mediators, etc. The intermediary between the two is of course the microcirculation. Unfortunately, no widely adopted clinical monitoring system is available to investigate the microcirculation consistently.

Improved clinical outcomes are primarily achieved when these endpoints are appropriately monitored to derive an effective, timely therapeutic intervention. In this talk we will address various static and dynamic methods for hemodynamic monitoring. Unfortunately, monitors have not consistently been shown to improve clinical outcomes e.g. mortality (Ospina-Tascon FA). Shoemaker, Kern, Berlauk and Boyd all demonstrated that optimizing hemodynamic parameters derived from the pulmonary artery catheter (PAC) resulted in improved clinical outcomes for high risk patients if instituted before organ failure.. However, subsequent clinical studies using the invasive PAC did not show specific patient benefits. These studies are often flawed and have been criticized for their lack of adoption of the *outcome axioms* discussed above (Vender). However, the negative PAC studies promoted the development of several other less invasive devices and techniques to derive similar parameters as the PAC (i.e. esophageal doppler, pulse contour analysis, pulse pressure variation, bioimpedance, bioreactance, partial CO2 rebreathing, transthoracic echocardiography, etc). It is still unclear as to whether these less invasive devices provide the accuracy needed to aid clinicians in the development of helpful therapies. Still, recent studies have demonstrated a clinical benefit in perioperative patients when using some of these noninvasive techniques coupled with GDT. Further discussion of the benefits and liabilities of these invasive and less invasive hemodynamic monitors will be discussed in this lecture.

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ANESTHESIOLOGY 2017
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Pediatric Anesthesia Outside the Operating Room; What Every Anesthesiologist Should be Prepared For

Kirk Lalwani, M.B., B.S., F.R.C.A., M.C.R.
Oregon Health and Science University,
Portland, Oregon, U.S.A.

Learning Objective 1
Summarize relevant pediatric sedation guidelines for anesthesia care outside the operating room.

Learning Objective 2
Analyze current evidence for the safe provision of pediatric anesthesia care outside the operating room.

Learning Objective 3
Identify salient patient characteristics associated with adverse events during procedural sedation.

Learning Objective 4
Discuss the potential risks of some common pediatric procedures outside the operating room.

Learning Objective 5
Utilize a 'Best Practices' approach to optimize outcomes following pediatric anesthesia care outside the operating room.

Introduction

The practice of pediatric sedation is an essential area of care for pediatric anesthesia providers. The need for pediatric sedation outside the operating room environment has increased exponentially over the last two decades. This is the result of continued development of sophisticated imaging and diagnostic technologies as well as other therapeutic measures that necessitate treatment in distant locations, or that are provided outside the operating room to improve efficiency and potentially decrease costs. In addition, regulatory requirements and guidelines issued by governing bodies and professional societies have mandated changes in practice to improve safety during and after pediatric sedation.

Research studies that have enrolled large numbers of pediatric patients undergoing pediatric sedation such as those published by members of the Pediatric Sedation Research Consortium (PSRC) have finally provided reliable data on the incidence of complications and the factors that may increase risk during pediatric sedation. Environmental and systems factors have been explored in the context of safety, and for the ability to rescue patients from critical events in non-operating room locations. The development of newer drugs in parallel with the recognition of the risks of older pharmacologic agents with long half-lives has undoubtedly changed the face of pediatric sedation practice by decreasing the incidence of side effects for patients, as well as the incidence of some adverse events.

This session will briefly explore current guidelines related to pediatric sedation, review evidence for safe provision of pediatric sedation care, highlight patient characteristics associated with adverse events, and review some common pediatric procedures outside the operating room with a 'Best Practices' approach.

Guidelines

In 2016, joint guidelines for the care of pediatric patients before, during, and after sedation were updated by the American Academy of Pediatrics and the American Academy of Pediatric Dentistry. The American Society of Anesthesiologists Task Force on Anesthetic Care for Magnetic Resonance Imaging issued an update to its practice advisory for anesthetic care during magnetic resonance imaging in 2015, both of which are very relevant to the practice of pediatric sedation outside the operating room.

Safety

Several recent studies have highlighted both the safety of pediatric sedation with highly trained and motivated teams, as well as the potential for adverse events even with optimal resources and experienced providers. In addition to more well-known risk factors such as ASA Physical Status 3 or 4 and younger age (neonates and infants), we now have evidence of the association between premature birth and an increased risk of complications during sedation in older children and teenagers. One recent large study found a < 1:10,000, incidence of aspiration during pediatric sedation with no relationship to NPO status. An area of ongoing concern is the tragic epidemic of deaths in dental clinics in the U.S., many of which had questionable care and monitoring and were, therefore, likely avoidable.

Risk

Risk in pediatric sedation is multifactorial, and may be related to patient factors, provider factors, polypharmacy, inadequate monitoring, an unfavorable environment (which includes equipment, team dynamics, and rescue from critical incidents), or a combination of factors. In addition to the dental clinic sedation tragedies mentioned above, the MRI suite is a potentially dangerous location for pediatric sedation due to a variety of factors combined with the strong magnetic field that is a risk to patients and providers. Sedation in the radiotherapy suite often requires careful positioning and reliable immobility, where patients need to be monitored remotely. All these settings have unique challenges that require a flexible approach to providing care in a safe and acceptable manner.

Best Practices

While it is unlikely that a set of universal ‘Best Practices’ can be customized for any practice setting, there are some principles related to preoperative assessment, monitoring, provider experience and training, sedation agents, and a regular quality improvement process that are fundamental for the provision of safe pediatric sedation care. This session will summarize a set of generally applicable ‘Best Practices’ that form the cornerstones of high quality sedation care based on available evidence, guidelines, and practice advisories.

ANESTHESIOLOGY 2017
BOSTON OCTOBER 21-25

Low-Tech Simulated Emergency Drills Made Easy

Scott Watkins, M.D. — **Nashville, TN**
Paul Preston M.D. — **San Francisco, CA**
Steve Howard, M.D. — **Stanford, CA**
William Berry, M.D., M.P.H., M.P.A. — **Boston, M.A**

Uncommon, stressful, high acuity critical events in the operating room challenge clinicians' memory, cognitive function and capacity to lead an effective team response. The rarity of these events demands practice. Emergency drills are a standard readiness tactic in most high reliability organizations such as aviation, nuclear power and others.

Effective and low cost simulation experiences are within the reach of nearly every facility, with or without a dedicated simulation facility.

This session will focus on practical aspects of conducting low technology emergency simulations and include a live demonstration of such a drill and a demonstration with tutorial on the key elements of debriefing.

ANESTHESIOLOGY 2017
BOSTON OCTOBER 21-25

Mechanical Device Therapy for Heart Failure: Friend or Foe Review of device therapy and updates on perioperative management

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Katja R. Turner, MD **Columbus, OH**
Marc E. Stone, MD **New York, NY**

From Decision to Placement

Clinical context:

Heart failure (HF) affects approximately 5.8 million of the U.S. population with a yearly incidence of 650,000 new cases, more than 1 million hospitalizations, 300,000 deaths and a price tag of ~$40 billion.[1] About 300,000 patients are refractory to optimal medical management, also known as stage D heart failure.[2, 3] Current treatment options include optimal medical management, mechanical circulatory support (MCS) therapy with short and long-term devices, and heart transplantation. Although heart transplantation may be considered the ultimate therapy with a median survival >10 years, very few organs are available for transplantation.[4]

Mechanical Circulatory Support (MCS):

Left ventricular assist device (LVAD) therapy had a major breakthrough with the publication of the "Randomization of Mechanical Assistance for the therapy of Congestive Heart Failure (REMATCH)" trial in 2001. The "REMATCH" trial demonstrated superior survival at 12 months (52%/23%) and 24 months (25%/8%) in patients ineligible for cardiac transplantation who were supported with a mechanical LVAD compared to patients treated with optimal medical management.[5] The use of LVAD therapy soon expanded to include bridge to decision (BD), bridge to recovery (BR), bridge to transplant (BT) and destination therapy (DT). Over the next decade, newer devices were developed and survival improved. While the majority of the long-term devices are still implanted as BT, the indication as DT was recently reported to be 46%.[6] Mancini et al. describe a 3-step algorithm when evaluating stage D heart failure patient for suitable therapy:[7]

1. Eligibility for transplantation
2. Eligibility for MCS therapy as destination therapy (DT)
3. Palliation if neither therapy is appropriate

The center for Medicare and Medicaid services (CMS) defines eligibility for DT as the patient meeting all of the following conditions[8]:

1. Congestive heart failure (CHF) refractory to medical management for at least 45 out of 60 days, or dependence on intra-aortic balloon pump support ≥7 days or intravenous inotropic therapy ≥14 days
2. Left ventricular ejection fraction (EF) <25%; and
3. Functional limitations with peak oxygen consumption ≤14ml/kg/min unless treated with an intra-aortic balloon pump, inotrope dependency, or simply unable to perform exercise testing

An Interagency Registry for mechanically assisted circulatory support (INTERMACS) sponsored by the National Heart Lung and Blood institute was created in 2006, prospectively enrolling patients treated with LVAD's. Based on collected data, annual reports on the state of MCS therapy are published. According to the last report, the vast majority of long-term MCS devices implanted in the U.S. are continuous flow devices, predominantly the 2nd generation device HeartMate II® (HM II; St. Jude Medical, St. Paul, MN, USA) and the 3rd generation device Heartware HVAD® (HeartWare, Framingham, MA, USA, a subsidiary of Medtronic) with a 12/24-month survival of ~80/70-%

respectively.[6] The improvement in survival is due to a combination of improved device design (fewer movable parts), increased device experience, as well as a change in patient selection. The INTERMACS registry grouped the patients with Stage D HF into seven groups according to their symptom profiles. A numeric increase in INTERMACS group or profile correlates with a decrease in severity of symptoms (Table 1).

Table 1. INTERMACS Profiles

INTERMACS 1	Patients in critical cardiogenic shock despite maximal therapy
INTERMACS 2	Patients with deteriorating symptoms despite therapy with inotropes
INTERMACS 3	Patients in stable conditions, but dependent on therapy with inotropes
INTERMACS 4	Patients with symptoms at rest , no inotropes
INTERMACS 5	Patients unable to exert themselves
INTERMACS 6	Patients with limited ability to exert themselves
INTERMACS 7	Patients with advanced NYHA class III symptoms

A decade ago, the majority of MCS devices (>40%) were implanted in patients in cardiogenic shock (INTERMACS 1). Experience has shown that implantation of a long-term VAD as "rescue intervention" in a patient in critical cardiogenic shock (INTERMACS 1) results in poor long-term survival. Device placement in this patient profile group declined to 14%, and currently, MCS devices are predominantly implanted in inotrope-dependent, but more stable patients (INTERMACS 2 and 3).[9] Although to date >14,000 MCS devices have been implanted in the U.S., [6] this therapy modality remains plagued by perioperative and post-operative complications. Significant perioperative challenges during device placement include bleeding, profound vasoplegia, and right ventricular failure (RVF). While bleeding and vasoplegia present significant problems during the perioperative care, RVF remains the biggest challenge with significant morbidity and mortality regardless of the MCS device indication.

Right Ventricular Failure (RVF):

The reported incidence of RVF ranges from 5-44%, with a wide range partly due to varying definitions of RVF.[10, 11] Conceptually, post implantation RVF is defined as the continued need for inhaled pulmonary vasodilators, inotropes, or right sided MCS device therapy. Definitions differ mainly in the length of time (1 vs 2 weeks) of continued medical therapy (inotropes and/or pulmonary vasodilators) supporting the right ventricle. Once RVF requires MCD support, survival rates of the LVAD recipient are decreased (50 to 80 %) at 12 months. [6]
Robert Kormos nicely described the dilemma of RVF after LVAD placement in an editorial in 2014:[12] He called the LVAD both "beneficial and detrimental for the right ventricle (RV)". While a LVAD achieves beneficial RV afterload reduction, geometrical changes of the RV secondary to the shift of the interventricular septum with left ventricular decompression in combination with increased RV preload present a significant strain on the already impaired RV. Many investigators tried to identify predictors of RVF, as multiple scoring systems were developed (e.g. Matthews scoring system, Fitzpatrick scoring system, or Drakos scoring system).[13, 14, 15] A recent review of the literature pertaining to the prediction of RV failure over the last 20 years described only a few predictors that held true over time with limited sensitivity and specificity including:[16]

1. Laboratory data
    a. Elevated International normalized ratio (INR)
    b. Elevated white blood cell count (WBC)
    c. Elevated N-terminal pro-brain natriuretic peptide (NT-proBNP)
2. Hemodynamic data
    a. Increased central venous pressure (CVP)
    b. Decreased right ventricular stroke work index (RVSWI)
3. Echocardiographic data

   a. Qualitative evidence of moderate to severe RV dysfunction
   b. Increased RV/LV diameter ratio
   c. Reduction in longitudinal RV strain
4. Preoperative mechanical ventilation
5. Preoperative continuous renal replacement therapy

Though the overall incidence of RVF requiring the placement of a Right ventricular assist device (RVAD) has declined, it remains the Achilles heel of MCD therapy.

Perioperative Management:

The current evidence guiding the perioperative management of LVAD placement is limited, but describes the use of invasive monitoring (Arterial line and Central venous catheter with or without pulmonary artery catheter), adequate IV access, perioperative transesophageal echocardiography (TEE) evaluation/monitoring, and anesthesia providers familiar with clinical issues related to patients with advanced HF and LVAD placement during induction, the surgical procedure (including separation from bypass), and activation of the assist device. [17, 18, 19]
The foundation of optimal perioperative care of the patient presenting for LVAD placement builds on the preoperative optimization of the patient.

Optimization includes:

1. Treatment of acute decompensated HF with optimal diuresis while avoiding hypovolemia and inotropic support (phosphodiesterase inhibitors, dobutamine or intra-aortic balloon pump)
2. Optimization of end-organ function (e.g. kidneys, liver)
3. Diagnosis and treatment of infections
4. Minimizing anticoagulation as safely tolerated
5. Assessment and optimization of RV function

Bleeding must be anticipated due to either anticoagulation of the patient and/or redo procedures on the chest. Targeted patient blood management (incl. point of care testing) and meticulous surgical technique are of the essence. Perioperative hemodynamic stability must be maintained with careful titration of fluids, anesthetic agents (induction/maintenance of anesthesia), narcotics, inotropes (Epinephrine, Phosphodiesterase inhibitors, Dobutamine), vasoconstrictors (Vasopressin, Norepinephrine, Phenylephrine) and inhaled pulmonary vasodilators to maintain biventricular function.
Perioperative echocardiography is used to assess RV function and to rule out structural defects in need of surgical correction (e.g. closure of atrial or ventricular shunts, correction of significant aortic or tricuspid valve insufficiency, and mitral valve stenosis) prior to device placement. Upon activation of the VAD, TEE is used to evaluate inflow cannula position, outflow graft patency, LV volume status, RV size and function, as well as the position of the interventricular septum.
RV dysfunction is initially treated by controlling LVAD speed and decompression of the LV and hence the position of the interventricular septum. Factors affecting the vasomotor tone of the pulmonary vasculature, and therefore worsening pulmonary hypertension (hypoxia, hypercarbia and acidosis), are corrected. Pharmacological agents, such as inotropes, vasoconstrictors, and pulmonary vasodilators are further utilized to support the RV. It is critical though to consider the need for right sided temporary device therapy in the early decision process.

From Placement to Destination

There are more patients living longer with LVADs now than at any previous point in history. According to the latest INTERMACS Annual Report,[6] overall all-comer survival with a durable MCS device now approaches 80% at one year, and 4 year survival now approaches 50%. With improved survival, there has been a dramatic surge in the number of heart failure patients implanted with VADs on an annual basis, and there are now over 2,500 VAD implants per year in the U.S. alone. Currently, the two approved durable devices commonly used in the U.S. are the HM II and the HVAD. Other durable devices that ostensibly address issues with the current devices remain in clinical trials in the U.S.

Though this "next generation" of implantable LVADs portend major advancement in several important ways over the first generation of pulsatile devices (e.g., the HM I LVAS, the Novacor, etc), and we have seen a dramatic decrease in the rates of specific complications associated with VAD support (e.g., mediastinal bleeding, RV failure), INTERMACS data indicate that the total burden of "adverse events" (AEs) has not actually decreased, because the rates of other AEs have now increased (including stroke, renal failure, respiratory failure, "infection", "psychiatric episodes", "bleeding"). Further, the rates of AEs specific to current devices (e.g., pump thrombosis, GI and intracerebral bleeding) vary widely from one report to the next, and the actual incidence and prevalence of specific issues with each device are still being determined. Major published trials (e.g., MOMENTUM 3,[20] ENDURANCE,[21] and REVIVE-IT[22]) and independent analyses (23,24) compare and contrast various devices and statistical methodologies regarding AEs, and outline specifically the current issues of the day. Table 2 discusses select, current "issues" with presently approved, durable, implantable devices.

Unfortunately, each manufacturer reports the rates of AEs (or freedom therefrom) with their device differently (e.g., incidence at a given time point after implantation versus "event rates per patient year"), making direct comparison of the various devices difficult. Further, combinations of AEs (or freedom therefrom) are now often reported as composite end-points (especially in studies intended to demonstrate "non-inferiority"), which tend to obscure the impact of any individual complication. It is also important to understand that some published and/or reported analyses have used historical cohorts and/or INTERMACS data as control sets, and one should always bear in mind that improvements to device design and/or to patient management protocols over the years may make it challenging to compare outcomes with current devices to historical controls implanted with prior generations of the devices.

Table 2. Present Status of Adverse Events with Currently Implanted LVADs:

COMPLICATION	CURRENT STATUS
Pump Thrombosis	• The rate of confirmed HM II pump thromboses at 3 months after implantation rose from approximately 2.2% in March 2011 to 8.4% by January 2013,[24] and a 2014 publication reported that pump thrombosis was also a problem for the HVAD[25] • INTERMACS data revealed that freedom from pump thrombosis at 6 months fell from 98% in 2010 to 92% in 2013 (n = approximately 9800 patients) and then improved to 95% through June 2014[26] • The MOMENTUM 3 trial (conducted between September 2014 and October 2015) reported a 10.1% rate of HMII thrombosis at 6 months[21]
GI bleeding	• GI bleeding in the first 5 years following CF LVAD implantation has a reported incidence between 0% - 31% [27-32]
Stroke	• The ENDURANCE trial reported stroke rates of 29.7% with the HVAD and 12.1% with the HMII[21]
Driveline Infection	• The cumulative risk of driveline infection for both the HMII and the HVAD has been reported at 7%, 20%, and 29% at 1, 3, and 5 years, respectively[33]
Driveline Failure	• HMII pump exchange due to driveline wire fracture and/or the "short-to-shield phenomenon" has been reported[34]

Destination Therapy (the use of an LVAD as a final, permanent management strategy for end-stage heart failure) is now the most common indication for LVAD implantation (increased to 45.7% of all implants in 2014 compared to 14.7% in 2006-2007, and 28.6% between 2008-2011), followed by BT (the classic indication for durable LVAD support) and "Bridge-to-Candidacy" (BC) (for transplantation, as the time spent on LVAD support often allows for improvement in multisystem organ function to the point where transplant ineligible patients can become eligible). Thus, perhaps not surprisingly, there has been a dramatic increase in the number of non-cardiac surgical (NCS) procedures performed on LVAD-supported patients each year.

Non-Cardiac Surgery (NCS) for the LVAD-Supported Patient:

The most common elective NCS procedures now performed on LVAD-supported patients appear to be endoscopies (upper and lower) for both screening and interventional purposes, but regardless of the complexity of the planned procedure, the preanesthetic assessment of and the perioperative considerations for the LVAD-supported patient are the same.

Preoperative Assessment

The preoperative clinical status of an LVAD-supported patient depends primarily on the extent of end-organ damage sustained during the low-cardiac output state existing prior to VAD implantation, any post-implantation complications, the present surgical problem, and any other comorbidities. Even though some patients supported by an LVAD are ambulatory, varying degrees of renal, hepatic, pulmonary, and/or central nervous system insufficiency may exist, so a review of all major organ systems is essential, even for minor procedures.

If you have questions, concerns, or areas of unfamiliarity regarding the implanted device, preoperative discussions with a knowledgeable colleague, the physician managing the VAD, the surgeon, and/or dedicated VAD staff are strongly encouraged. If you are going to be requesting assistance, it is usually very helpful for your consultant to know what device is present, so ascertain the name of the VAD as part of your preoperative assessment. It is common for patients with heart failure to have a pacemaker and/or ICD implanted, so it is reasonable to also obtain the necessary information about that device. Perioperative management of pacemakers and ICDs is the same as for any patient.

Peri- and Intraoperative Considerations

- Appropriate perioperative anticoagulation. Preoperative planning to ensure appropriate anticoagulation throughout the perioperative period is critical. An INR of approximately 2 – 3x normal is required to prevent thrombus formation and potential embolism with both the HM II and the HVAD. LVAD patients are usually maintained on warfarin and aspirin, though those with demonstrated aspirin-resistance may be taking another antiplatelet agent. In elective but major cases where bleeding risk is substantial, warfarin can be discontinued and/or the patient can be bridged to surgery with heparin that then can usually be tapered down to the lower limits of manufacturer's recommendations (which may even allow for brief periods without any) for the immediate perioperative period. Aspirin should likely be continued. Most endoscopies and many general surgical procedures can be safely performed with mild levels of anticoagulation. Neurosurgical and ophthalmological procedures will require careful planning with input from the physician managing the VAD and the surgeon. Point-of-Care tests of clotting (e.g., PTT, INR, ACT, etc.) and viscoelastic tests (e.g., ROTEM, TEG) can aid management and are helpful to guide infusions of FFP, cryoprecipitate, and/or platelets when needed.
- PLUG IT IN! Fully charged, modern, wearable LVAD batteries typically last for 4-8 hours, depending on the number of previous charging cycles and the hemodynamic condition of the patient. Regardless, whenever feasible, one should keep the device plugged in and the backup batteries charged. As well, the full control console can be used only when the device is plugged in to main A/C power.
- Appropriate antibiotic coverage. Preoperative antibiotic coverage for most procedures often includes broad spectrum agents taking local flora into account. Coverage for gram negatives and anaerobes is prudent for intra-abdominal procedures. Anti-fungals should be considered in patients who may be at higher risk, which may include recent treatment with an antibiotic course or multiple indwelling catheters. Most infections associated with VADs tend to occur in the percutaneous tract through which the driveline exits but the VAD driveline itself should not be prepped with povidone-iodine containing solutions because these can result in breakdown of the plastic. When necessary, drivelines can be draped out of the field or covered temporarily with a sterile incise drape.
- Appropriate perioperative management of pacemakers and ICDs. Pacemakers and ICDs should be managed as they would for any other CIED patient undergoing the same procedure.
- Avoidance of hypovolemia. Though modern LVADs provide continuous (non-pulsatile) flow, most supported patients will regain pulsatility of their circulation once the volume and pressure overloads are removed from their failing LV and they are stabilized on their device. The maintenance of adequate volume status is paramount throughout the perioperative period to ensure hemodynamic stability under anesthesia

and/or sedation. Optimization of LV volume will maintain contractility through Starling's mechanism, while inadequate LV volume may result in "a suckdown event" (leading to low VAD output and hypotension). The clinical screen on the VAD console provides information that can be used to help optimize volume status (e.g., the Pulsatility Index of the HM II, the flow curves of the HVAD…the clinical screens of these common devices will be discussed in detail during the lecture). Echocardiography will rarely be needed but can be helpful where hypovolemia must be distinguished from RV dysfunction as the cause of inadequate volume in the LV.

- Appropriate monitoring. Standard ASA monitors can be used as long as sufficient pulsatility is maintained. Invasive arterial pressure monitoring is prudent for cases involving large fluid shifts or anticipated blood loss where pulsatility may be intermittently lost. Cerebral oximetry has become a popular backup "measure of oxygenation" in cases where pulse oximetry may become unreliable due to intermittent loss of pulsatility. Echocardiography will rarely be needed but can be helpful where hypovolemia must be distinguished from RV dysfunction as the cause of inadequate volume in the LV. The potential benefits of monitoring central pressures must be weighed carefully against the risks of central venous cannulation (including central line associated bacteremia).
- Anesthetic agents and techniques. The requisite anticoagulation associated with mechanical circulatory support limits the potential to use central neuraxial blocks, but superficial regional blocks performed under ultrasound guidance can often be used, as can intravenous extremity blocks (e.g., Bier block). Notwithstanding, most LVAD patients will receive sedation or general anesthesia as befitting the planned procedure. The intubation and extubation criteria for the LVAD-supported patient are identical to those for any other patient undergoing the same procedure.
- Coordination with VAD personnel. It is important to involve the "VAD team" at all stages of the perioperative period. Knowledgeable VAD personnel can be extremely helpful during transport to and from the OR and/or recovery location, and can be very reassuring to intraoperative teams and the recovery staff who only infrequently encounter VAD-supported patients.

Postoperative Considerations

- Appropriate recovery location. Excessive apprehension on the part of the receiving physicians, nurses, and/or physician extenders in the recovery location is not in the best interest of the patient. It is strongly encouraged to clearly outline the goals of management and of hemodynamics with the receiving team, and provide education as needed.
- Plug it in. Transport to the recovery location will be on battery power. It is prudent to reconnect the VAD to mains A/C power and utilize the VAD control console in the recovery location.
- Continue optimization. Assurance of optimized volume status must continue in the postoperative period.
- CIEDs. Baseline pacemaker and ICD settings should be restored prior to discharge from the monitored recovery location
- Pain management! Excellent pain management is essential for many reasons, but in the case of an LVAD, it is especially important as pain may increase pulmonary vascular resistance, which could place an unnecessary pressure load on the unsupported RV.

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Obesity in the Operating Room: How Big a Problem?

Stephanie B Jones, MD **Boston, MA**

Obesity is commonly defined as a body mass index (BMI) > 30 kg/m2. It is commonly perceived that the higher the BMI, the higher the risk of perioperative complications. But how big a problem is obesity, really?

The Airway

While the patient with obesity is traditionally regarded as at high risk of difficult intubation, the evidence in the literature does not necessary bear this out. Weight alone is not predictive of difficult intubation, as variously defined in the literature, and BMI is weakly predictive at best. The traditional risk factors still hold when applied to the patient with obesity: presence of obstructive sleep apnea (OSA), large neck circumference, and Mallampati classification 3 or 4. These items should be included as part of the airway history and physical in all patients, and certainly in the patient with obesity. In fact, one of the contributing factors in the 4th National Audit Project (NAP4) of the Royal College of Anaesthetists and the Difficult Airway Society, "Major complications of airway management in the UK", was failure to document an airway exam in an obese patient [1]. This implies failure to perform the exam; 17 of the 53 patients with obesity included in the audit did not even have a Mallampati class recorded. In the 2013 update of the ASA Practice Guidelines for Management of the Difficult Airway, obesity is similarly mentioned in the context of the airway history and physical, i.e. that there is observational correlation with difficulty [2].

Despite the perhaps lower than expected rate of difficult endotracheal intubation, the bariatric airway must still be respected. Obesity is a risk factor for difficult mask ventilation (MV). A 4 year observational study at the University of Michigan examined > 53,000 attempts at MV [3]. Of these, 2.2% were "difficult", defined as "inadequate to maintain oxygenation, unstable MV, or MV requiring two providers" and 0.15% were "impossible", "absence of end-tidal carbon dioxide measurement and lack of perceptible chest wall movement during positive pressure ventilation attempts despite airway adjuvants and additional personnel". BMI > 30 kg/m2 was predictive of difficult MV. Independent predictors of difficult MV overlap with difficult intubation criteria – OSA, Mallampati 3 or 4, neck irradiation changes and add male sex and beard.

Therefore, in the rare instance that intubation becomes difficult, our fundamental rescue technique of MV may also fail. One is then confronted with the realities of cardiopulmonary physiology of the patient with severe obesity. Increasing body mass requires an increase in cardiac output to supply oxygen to tissues. Recall that an increase in total body mass is accompanied not only by increasing adipose tissue, which is relatively poorly perfused, but also by increased well perfused lean body mass. While the body needs an increased oxygen supply, a decreased functional residual capacity (FRC) works in opposition to that goal, creating less reserve for apneic oxygenation during induction and intubation. Various maneuvers have been utilized to improve FRC during induction including application of continuous positive airway pressure or positive end expiratory pressure, 25-30 degree reverse Trendelenburg positioning and, more recently, high flow nasal oxygen. Studies are still ongoing as to the benefits of high flow nasal oxygen, delivered either via standard nasal cannula (5-15 L/min) or commercially available devices (humidified, up to 70 L/min), for the obese population in the perioperative context [4]. At least one study was able to demonstrate an increase in time before O2 saturation dropped below 95% after induction in a population of male patients with BMIs between 30 and 35 wearing 5L/min nasal O2 [5].

Another interesting and somewhat regional controversy is the use of succinylcholine versus nondepolarizing neuromuscular blockade when securing the airway in a patient with severe obesity. Obesity has been cited in older literature as a risk factor for aspiration; more recent work has shown this is likely due to prolonged airway manipulation rather than obesity per se. Thus the rationale for choosing succinylcholine is more rapid access to the airway, avoiding the need for potentially difficult MV, not necessarily as part of a rapid sequence induction. Opponents of succinylcholine cite the well-known side effects (postoperative myalgias, arrhythmia) as well as increased oxygen utilization caused by fasciculations, creating a situation where more rapid desaturation could occur. This has been demonstrated in a study from China in overweight patients where the time from administration

of neuromuscular blockade to a SpO2 of 92% decreased from 329 seconds for rocuronium (0.9 mg/kg) to 283 seconds for succinylcholine (1.5 mg/kg) [6]. Recovery upon initiation of ventilation to SpO2 97% was also prolonged (36 vs 43 seconds). The dose of succinylcholine is higher than commonly used; it is unclear whether this may have affected the results.

While a great deal of attention is paid to induction and intubation, with optimal positioning, preoxygenation and availability of airway adjuncts, the risks of emergence and extubation for the patient with obesity remain, in my opinion, underappreciated. An ASA Closed Claims Project study published back in 2005 found that 37% of brain damage and death claims related to induction of anesthesia involved obesity as a contributing factor, compared to 67% of extubation claims [7]. Similar data emerged from the later NAP 4 audit, with 46% of airway events during emergence or recovery occurring in obese patients. Ensuring full reversal of neuromuscular blockade, utilization of multimodal, opioid-sparing analgesic regimens, and appropriate screening for and treatment of OSA may improve our performance in this area.

The Obese Outpatient

The anesthesiologist practicing in an ambulatory surgery center (ASC) will increasingly face the question of whether a body mass index (BMI) or weight cut-off exists (or should exist) for patients in that setting. According to data derived from the Behavioral Risk Factor Surveillance System (BRFSS), an estimated 15.5 million adults in the United States (6.6% of the population) had a BMI $\geq$ 40 kg/m^2 in 2010 [8]. Regression modeling from the BRFSS data predicts a severe obesity prevalence of 11% by 2030, and a 42% prevalence of obesity (BMI $\geq$ 30 kg/m^2) [9]. If obese and severely obese patients are deemed ineligible for ambulatory anesthesia in significant numbers, timely access to surgical care could be compromised. Thus is it important to understand when and which patients with obesity may safely be cared for in the ambulatory setting.

The answer can be quite simple when total body weight is the limiting factor. Critical equipment such as stretchers, operating tables, and radiology imaging tables must be able to bear the weight load of the patient. Tables and stretchers should be clearly labeled with weight limits, which frequently differ depending on table position. Additional facility items must accommodate the larger patient's weight and breadth: CT and MRI gantry apertures, bathroom commodes, cardiac chairs, and waiting room seating, for example. [10]

The BMI limit, however, requires a more complex response. Although attempts have been made, the literature is currently of insufficient quality and quantity to provide a definitive BMI above which alternate surgical arrangements should be made in every case, or below which perioperative complications could be avoided with near certainty. Obesity has been identified as a risk factor for perioperative complications after outpatient surgery in several, often retrospective, studies. Sieffert et al [11] used discharge data from four states (California, Florida, Nebraska, and New York) to examine complications following outpatient liposuction, abdominoplasty, blepharoplasty, and reduction mammoplasty. Of 47741 patients cared for in 978 ASC or outpatient surgery departments, 2052 (4.3%) were overweight or obese. 7.3% had at least one hospital-based encounter within 30 days of discharge, compared to 3.6% in the non-obese/overweight group. The highest risk group was those undergoing abdominoplasty with three or more comorbid medical conditions. 32% presented for an acute care encounter compared with 14% for those with 2 or less comorbidities. Similarly, Ranum [12] et al studied closed ambulatory surgery claims from a single insurer between 2007 and 2012. The most frequent injuries attributed to anesthesia providers, aside from dental injury, were death and nerve damage. Obesity was identified as the most frequently contributing patient factor, impacting outcome in 15% of cases. The presence of obesity influenced surgical difficulty, obscured anatomy during the placement of neuraxial and peripheral regional blocks, and affected airway management complications at the time of initial or rescue intubation, as well as following extubation. The larger American College of Surgeons National Surgical Quality Improvement Program (NSQIP) supports these findings. [13] Nearly 250,000 patients were identified as having undergone day case surgery between 2005 and 2010. Of these, 232 (0.1%) were found to have early perioperative morbidity or mortality. When controlled for surgical complexity, seven independent risk factors for this early morbidity and mortality emerged. Two were overweight BMI (BMI $\geq$ 25 kg/m^2), with an adjusted odds ratio (AOR) of 1.58 (CI 1.07-2.35), and obese BMI (AOR 2.02, CI 1.37-2.98).

Contrast the above examples with a number of published case series touting successful outpatient performance of procedures not thought to typically fall into the ambulatory category. Laparoscopic sleeve gastrectomy (LSG) has quickly become the most common weight loss surgery in the United States, constituting 54% of the 196,000 bariatric procedures performed in 2015 [14]. A French group prospectively studied 100 patients meeting criteria for day case LSG [15]. Patients were ineligible for day case surgery if their BMI exceeded 60 kg/m^2, if they had obstructive sleep apnea (OSA), cardiac disease, or poorly controlled diabetes, or lived over an hour from the hospital. 416 patients were screened during the study period; 24% met inclusion criteria and all consented to the day case procedure. Unplanned overnight admission was the primary endpoint. Eight patients were admitted for a variety of reasons including pain, nausea, somnolence in the day surgery unit, difficult intubation, and discomfort following the mandatory postoperative upper GI exam. Although this study lacked a true control group, there were no significant differences in major complications or hospital readmissions between the day case group and standard care group. Billing et al [16] published a series of 250 patients undergoing LSG at a single ASC. The BMI range was wide, between 29 and 71, but patients were excluded if weight was greater than 450 pounds. Other exclusion criteria included anticipated surgical time of over 2 hours, significant medical comorbidities that would require monitoring greater than 23 hours, and impaired mobility. Only 2 patients (0.8%) required admission, both related to untreated OSA. Nine (3.6%) were readmitted within 30 days. Interestingly, patients were discharged from the ASC with a saline-locked IV in place, and received 1-2 liters of intravenous fluids during their visit on postoperative day 1. The authors, two of whom own the ASC, describe strengthening the patient selection criteria following this series. They now observe all OSA patients overnight, and enforce an upper BMI limit of 50 kg/m^2 "for purposes of reducing airway concerns". Common to both of these reports is multimodal analgesic regimens, aggressive prophylactic antiemetic therapy, and an emphasis on appropriate patient selection.

Indirect evidence of the importance of patient selection can be found in a study by Rosero and Joshi [17]. They derived a propensity-matched cohort of morbidly obese and non-obese patients from the 2006 National Survey of Ambulatory Surgery. Only 0.32% of procedures in the database were performed on morbidly obese patients, despite a prevalence of morbid obesity of approximately 4% in the overall population that year. Most of the procedures were performed in a hospital outpatient department, as opposed to an ASC. The low number of obese patients in the database and choice of setting implies conservative patient selection. Given the apparent caution, it is not surprising that no difference was found between the groups in postoperative adverse outcomes or delayed discharge.

Few studies have attempted to probe whether the degree of obesity makes a difference. Kakarla et al compared bariatric surgical patients with BMI < 50 kg/m^2 versus ≥ 50 kg/m^2 (super obese) [18]. These were laparoscopic but not necessarily ambulatory procedures. The super obese patients had a significantly higher incidence of a variety of postoperative complications including wound infections, myocardial infarction, pulmonary embolus, sepsis and 30 day mortality. A study by Morton et al [19] from the Bariatric Outcomes Longitudinal Database (BOLD) investigating the impact of length of stay on 30 day outcomes after laparoscopic Roux-en-Y gastric bypass was able to demonstrate a significant increase in 30 day serious complications when patients with BMIs between 50 and 70 kg/m^2 were compared to those with BMIs under 50 kg/m^2. The odds ratio after adjusting for covariates was 1.42, CI 1.15-1.74.

The key for deciding on appropriateness for ambulatory surgery does not depend solely on BMI. Joshi et al, on behalf of the Society for Ambulatory Anesthesia (SAMBA) Committee on Clinical Practice Guidelines, make several general recommendations after stating that the evidence is too weak to support creation of a specific practice guideline [20]. They suggest, based on a review of 23 studies, that the super obese may be at higher risk and caution must be used when considering ambulatory surgery; that patients with BMI ≤ 40 kg/m^2 may be appropriate candidates for outpatient surgery so long as comorbid conditions are optimized; and that those with BMIs between 40 and 50 kg/m^2 are in a relative gray zone. These patients should be considered for ambulatory surgery on a case-by-case basis, after careful assessment and optimization of comorbidities, taking surgical site and acuity into account and designing an anesthetic plan that minimizes potential complications.

The Obesity Paradox

Several studies over the past decade have demonstrated what is commonly referred to as the obesity paradox – that mild to moderate obesity is relatively protective against mortality after events ranging from non-cardiac surgery to

myocardial infarction, percutaneous coronary intervention (PCI), and ICU admission. For example, Mullen et al [21] in 2009 examined the NSQIP databased and found an odds ratio of 0.73 for death in patients with Class II obesity (BMI 35-40) relative to normal weight patients, despite an increase in morbidity (primarily wound infection) as BMI increased. In multivariate analysis, obesity was an independent predictor of lower major adverse cardiac events at 12 months after PCI in an Australian study [22].

Ideas abound as to the possible reasons behind this apparent paradox. One is reverse causality, in this case that weight loss in induced by illness, so obese patients are healthier. A population based study from 2014 supports this concept [23]. All-cause mortality over time was tracked for BMI at time of the survey compared to maximum BMI. When maximum values were used, 33% of mortality was attributed to obesity, compared to just 5%. A second possibility is that the data simply isn't reliable because BMI does not accurately reflect obesity [24]. Body composition changes as we age, with a relative increase in body fat and decrease in muscle mass. It does not reflect the amount of visceral (versus subcutaneous) fat, and in many studies weight is self-reported or retrospectively documented. Waist circumference has been proposed as a better reflection of obesity and metabolic health, but is rarely included in typical databases, often the favorite mining ground for obesity outcome studies. Finally, it is clear that patients with obesity are a heterogeneous population. Some, even in the super obese BMI range, are metabolically "healthy". Metabolic syndrome impacts perioperative outcomes in general. Those studies that demonstrate no difference between non-obese and obese patient outcomes may have a disproportionate number of patients in the obese group without metabolic syndrome due to patient selection criteria.

Metabolic syndrome

Metabolic syndrome (MetS) is distinct from simple obesity, with an increased risk of type 2 diabetes mellitus and cardiovascular disease. Definitions vary by specialty group and guideline, but in general include:

- Increased waist circumference
- Hypertension
- Increased serum triglycerides
- Decreased serum HDL
- Impaired fasting glucose

MetS has been shown to effect perioperative outcomes. Glance et al [25] used a modified definition of MetS (obesity, hypertension, diabetes) to retrospectively examine non-cardiac surgical outcomes in >300,000 patients in the NSQIP database. Patients who met their criteria had a 2-3 fold increase in cardiac adverse events, 1.5-3 x pulmonary events, 3-7 x acute kidney injury, and 2 x CNS events. Schumann et al [26] looked specifically at pulmonary outcomes in the BOLD database. 12.7% of over 20,000 patients met criteria for MetS and had increased odds of pneumonia, respiratory failure, ARDS, pleural effusion and atelectasis. The composite pulmonary adverse events odds ratio was 1.87 (1.65-2.13).

Adipose tissue is an endocrine organ and, at least in some indivduals, creates a state of chronic, low grade inflammation. Fat secretes adipokines, including tumor necrosis factor alpha, C-reactive protein, and interleukin-6, all of which contribute to the inflammatory milieu [27]. Visceral fat is felt to be more pro-inflammatory, with greater macrophage infiltration. An increased proportion of visceral fat is often cited as one reason why cardiovascular disease occurs at lower BMIs in Asian populations relative to Caucasian [28].

The question remains as to how best use this information in the perioperative period. With appropriate preparation the vast majority of patients with obesity will suffer no adverse outcomes. But how can we preemptively identify those at higher risk due to MetS or other factors, and how should our anesthetic plan be altered to prevent adverse outcomes? BMI is convenient, but insufficient. Future research that will help clinicians discern which obese patients need higher levels of perioperative care should be made a priority as the number of patients with obesity continues to rise in the US and elsewhere.

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