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Lies, Damned Lies and Anesthesia Myths

John F. Butterworth, IV, MD

INTRODUCTION

Physicians, scientists, journalists, and the lay public prefer a plausible explanation (particularly if accompanied by a molecular mechanism) to an admission of ignorance. As a result, unproven hypotheses, opinions and plausible guesses are repeated in lectures and textbooks and become embedded in the canon of our specialty.

We will consider a representative subset of unproven (and, in some cases, disproven) hypotheses and assertions during the course of this brief presentation. The reader should judge whether these old chestnuts arise from the scheming of “liars, damned liars, or scientific experts,” (using a description of unreliable witnesses attributed to Robert Giffen), and should decide whether they now deserve to be called out as anesthesia myths.1

RESUSCITATION TOPICS

Is Normal Saline “Normal” or Beneficial?

Intravenous fluid therapy arose in the 1800s as a means of combating dehydration from cholera, then became part of routine care for surgical patients in the 1900s.2 At present, the IV fluids of choice for adults in most surgical suites are either 0.9% (normal) saline or a “balanced” salt solution (Normosol, Plasma-lyte, or lactated Ringer’s (Hartmann’s) solution). The sad truth is that multiple lines of evidence demonstrate that use of 0.9% saline leads predictably to an increased incidence of hyperchloremia, a condition associated with worse outcomes (including longer lengths of stay and a greater likelihood of death).3,4 In the absence of hyperchloremic metabolic alkalosis there are sparse indications for large volumes of 0.9% saline, and no good reasons to use 0.9% saline as a routine maintenance solution.5

Cricoid pressure Improves patient safety during emergency intubations

Cricoid pressure was introduced to medicine by Brian Sellick in 1961.7 In 26 patients considered at risk for aspiration, no regurgitation occurred during or after application of cricoid pressure in 23. In 3 patients, regurgitation occurred only after cricoid pressure was relieved following tracheal intubation. Sellick surmised that cricoid pressure had prevented regurgitation from occurring before and during intubation in these 3 patients. Nevertheless, Sellick provided no details regarding induction drugs, ventilation, patient body habitus, or other relevant factors that might also explain his findings.7

Sellick made several key assumptions.

1. That the cricoid cartilage, esophagus, and anterior surface of the vertebral body would be in constant alignment;

2. That his maneuver would fully occlude the esophagus and would prevent gastric contents from refluxing past the cricoid;

3. That his maneuver would reduce the incidence of pulmonary aspiration associated with “full stomach” conditions;

4. That cricoid pressure had no adverse consequences.

Current data using computed tomography and magnetic resonance imaging techniques show that assumptions 1 and 2 are false.7 There are no outcome studies supporting assumption 3, but such studies likely would not be feasible given rates of medically consequential aspiration during emergency surgery of ≤1 per 1000. As for assumption 4, multiple studies have shown that cricoid pressure can worsen the clinician’s view of the airway during direct laryngoscopy.8 If one were to grade the quality of the evidence supporting the use of cricoid pressure using standards of the Oxford Centre for Evidence Based Medicine, a grade no better than D could be assigned.9 In a recent survey, only 30% of Swiss and 52% of Austrian anesthesiologists use cricoid pressure as part of rapid sequence induction.9 Nevertheless, some regard cricoid pressure both standard care and standard of care.

GENERAL ANESTHETIC TOPICS

Invasive monitoring increases hemodynamic stability during induction

Many books and oral examination candidates emphasize the value of invasive hemodynamic monitoring during induction of general anesthesia for “sick” patients. But is there any evidence that having information from a central line or a pulmonary artery catheter increases hemodynamic stability during induction? In a randomized comparison, inductions conducted without benefit of pulmonary artery catheter data required no more interventions to maintain stable hemodynamics than inductions “guided” by data from the pulmonary artery catheter.10 Moreover, placement of the pulmonary artery catheter after induction of general anesthesia took less time than when performed before induction. Finally, there are no convincing data showing that pulmonary artery catheterization reduces the likelihood of mortality in this or any other circumstance.11

A slow induction increases hemodynamic stability

Many clinicians recommend a “slow, careful induction” in cardiac and other sick patients. But, is there evidence that a slow induction results in fewer hemodynamic perturbations than a well-conducted rapid sequence induction? In patients scheduled for coronary artery surgery, rapid sequence induction with sufentanil and succinylcholine produced similar hemodynamics and necessitated no more interventions with vasoactive drugs or IV fluid boluses than a slower (2 min) opioid-relaxant induction or a very slow, careful (5–10 min) opioid-relaxant induction.12–14

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REGIONAL ANESTHETIC TOPICS

pKa predicts speed of onset of regional anesthesia

All local anesthetic compounds (save for benzocaine) in widespread clinical use have a tertiary amine nitrogen, the protonation of which is influence by the pH of its environment. The charged (protonated) form of the local anesthetic is less membrane permeable than the uncharged (neutral base) form of the compound.1 It has long been assumed that when two local anesthetic compounds are compared for speed of onset, the compound with the reduced pKa will have the faster onset of action, because after injection, a larger fraction of this compound will be in the neutral form as compared to the compound with the larger pKa. The only problem with this “truism” is that it is incorrect. It is true that lidocaine has a smaller pKa and a faster onset than bupivacaine. But, chloroprocaine has the largest pKa of all and it has the fastest onset of all local anesthetics, even faster than lidocaine, disproving the “rule.” Moreover, the pKa rule fails even when used to compare structurally similar compounds given that tetracaine has a smaller pKa than procaine or chloroprocaine, but has by far the slowest onset of these three drugs.

Methemoglobinemia and prilocaine

Methemoglobinemia has long been associated with prilocaine, the only local anesthetic that is metabolized to o-toluidine. According to many textbooks, prilocaine will reliably produce medically important degrees of methemoglobinemia when doses >600 mg are administered. Vasters et al. found that serious degrees of methemoglobinemia can arise after prilocaine doses as small as 400 mg in fit adult patients.2 Interestingly, in a North American study, the local anesthetic most commonly associated with dangerous methemoglobinemia was benzocaine.3

Interscalene blocks and general anesthesia

In 2000 a report appeared in Anesthesiology describing 4 patients who experienced disastrous neurological complications after undergoing interscalene blocks while anesthetized.4 The author suggested (and the suggestion was repeated in an American Society of Regional Anesthesia guideline) that “Interscalene blocks should not be performed in anesthetized or heavily sedated adult or pediatric patients.” But, does the evidence show that anesthetized or heavily sedated patients are more likely to have neurologic damage? There are case reports of nerve damage after interscalene blocks performed in awake patients. Children routinely undergo nerve blocks (including interscalene blocks) while anesthetized and infrequently experience nerve damage.5 Moreover, large series of interscalene blocks performed in patients receiving general anesthesia report an incidence of adverse neurologic events no more frequent than that reported after interscalene blocks performed without general anesthesia.6 Is it reasonable to issue a practice guideline based only case reports and opinions that, in effect, labels the use of deep sedation or general anesthesia before interscalene block as malpractice when there are large published series that provide contradictory evidence?

Intraneural injections and nerve damage

William S. Halsted, the first physician to perform brachial plexus blocks in North America, injected cocaine into nerves under direct vision. Yet most modern textbooks indicate that intraneural injections must be avoided because they will consistently result in persisting deficits. Recent articles tend to emphasize the differences between intraneural injections that disrupt nerve structure and those that do not. They also emphasize the fact that unintended intraneural injections commonly take place despite use of either ultrasound guidance, motor nerve stimulation, or both, and that awake patients most often will not report symptoms during these injections.8

CONCLUSIONS

There are many long-accepted practices and published guidelines in anesthesia that either are not supported or are contradicted by the available data. Myths and unproven hypotheses continue to masquerade as received knowledge in our specialty.

REFERENCES

14. Rathmell JP, Brooker RF, Prielipp RC, Butterworth JF 4th, Gravalle GP. Hemodynamic and pharmacodynamic comparison of doxacurium and pipecuronium with pancuronium
during induction of cardiac anesthesia: does the benefit justify the cost? Anesth Analg 1993;76:513–9
Controversies in Pediatric Anesthesia: Myth Busters to the Rescue

Peter J. Davis, MD

OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea (OSA) involving airway obstruction during sleep, hypoxemia and sleep disruption occurs in 1–3% of children,7,8 whereas in adults, it is diagnosed in 38% of men and 25% of women.7,8

In adults, the prevalence of OSA is increased in patients with diabetes, those older than 60 years of age, those who are overweight, have hypothyroidism, alcoholism and head and neck cancer.

The presentation of OSA in children and adults is different (Table 1). Adults frequently present with daytime somnolence and obesity, whereas children may have normal weight or failure to thrive, behavioral disorders and enuresis. In both adults and children, the presence of OSA has increased risks for surgery. Namely, increased episodes of oxygen desaturation, postoperative reintubation, arrhythmias, and hypertension. Because of these adverse outcomes, the American Society of Anesthesiologists has published guidelines for the perioperative management of OSA patients.9 Though the “gold standard” for diagnosis of OSA is polysomnography, in children the diagnosis of OSA is frequently made on the basis of symptoms. Snoring is a sensitive but not specific sign of OSA. Approximately 10% of children have primary snoring. Although primary snoring does not progress to OSA, 40% of snoring children will have OSA.1,4

In children, obstructive events generally occur in rapid eye movement (REM) sleep as opposed to adults in whom obstruction occurs in non-REM or equal amounts of REM and non-REM sleep. The definition of polysomnography-defined OSA can differ among sleep labs. The apnea-hypopnea index (AHI) is defined as the number of obstructive events per hour of sleep. RDI (respiration disturbance index) is the number of respiratory events and central apneas per hour (Table 2). An AHI of 0–1 is considered normal, 2–4 is mild OSA; 5–9 moderate, and an AHI higher than 10 is severe.

The essential component of OSA in children is increased upper airway resistance, the most common cause being adenotonsillar hypertrophy. Although the classic pediatric patient with OSA is generally underweight, as the epidemic of obesity increases and affects more children, obesity is increasing as a risk factor for childhood OSA. In the United States, it is estimated that 33% of children are overweight and 17% are obese.10 Craniofacial abnormalities are commonly found in children with sleep apnea (Table 3).

Chronic OSA generally results in pharyngeal collapsibility with obstruction of the airway and subsequent hypoxemia and/or hypercarbia. With chronic hypoxemia and hypercarbia pulmonary artery pressure increases, which can result in right ventricular hypertrophy and heart failure. Patients with OSA can also develop biventricular dysfunction. Increased sympathetic nervous system along with autonomic and endothelial dysfunction can result in systemic hypertension. With right ventricular dysfunction, the ventricular system can bulge into the left ventricle (LV) thereby decreasing LV volume and cardiac output and increasing LV end-diastolic pressure and left atrial pressure. In addition, OSA can result in large negative intrapleural pressure changes, increases in LV afterload and the development of pulmonary edema.

Anesthetic concerns for children with OSA secondary to adenotonsillar hypertrophy must focus on (1) age-appropriate cardiovascular issues and (2) postoperative respiratory issues. Most anesthetic drugs have been successfully used in children. However, Brown et al. have noted that recurrent hypoxemia in young children is associated with decreased opioid requirements.11 This finding has also been observed in rodents.12 Note is the association of the nadir O2, nighttime saturation with the dose of postoperative morphine (MS). Brown et al. have calculated a formula for the postoperative dose of morphine based on the patient’s age and nadir nighttime pulse oximetry saturation.

\[ MS(\text{mg/kg}) = 0.0007 \times \text{age(months)} + 0.0021 \times \text{SaO}_2\text{nadir} \% - 0.1138 \]

In addition to the intraoperative challenges, some of the more difficult issues involve the management of the pediatric OSA patient in the postoperative period. Issues of pain relief, antiinflammatory drugs (NSAIDs) use, and opioid sensitivity are significant. Pediatric patients with OSA have an increased risk for postoperative respiratory complications.13–15 Children younger than 3 years of age have twice the risk of postoperative respiratory complications as children 3–6 years of age.

In addition to the perioperative administration of opioids, pain control and maintaining hydration have become significant issues in the postoperative period after discharge from the hospital. Pain control with acetaminophen, opioids and NSAIDs have become the main components of at-home pain therapy. However, all of the drug types have significant side effects.16–18

The use of codeine both with and without acetaminophen has come under more intense scrutiny. Codeine is nonanalgesic and it needs to be metabolized to morphine in order for it to be effective. Codeine is metabolized through the CYP2D6 pathway. There are a number of polymorphic forms. Thus, there can be patients who are ultra-rapid and extensive metabolizers (thus prone to high levels of morphine) as well as poor metabolizers (patients who derive no analgesic benefit from the drug).

At home, death from respiratory arrest has been reported in a number of patients who turn out to be ultra-rapid or extensive metabolizers. Although evidenced-based reviews of the

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Controversies in Pediatric Anesthesia

Cochrane collaboration suggested that there is no risk of bleeding in the post-tonsillectomy adenoidectomy patient with NSAIDS, it is unclear if this applies to the use of ibuprofen.

How effective is adenotonsillectomy in children? Published studies have reached slightly different conclusions. In a study of 207 children (of which only one was obese) Guilleminault et al.19 noted that patients' postoperative polysomnograms indices improved compared to their preoperative values, but still 46% of patients had an AHI that was higher than 1. Of note was that risk factors associated with elevated AHI postsurgery included preoperative deviated septums, Mallampati scores of 3 and 4, retroposition of the mandible and enlargement of the inferior nasal turbinates.

In summary, OSA in children is different from adults. Though the most common cause in pediatric patients is adenotonsillar hypertrophy, adenotonsillectomy is not always curative but greatly improves the patient's symptoms. Whether it can influence the effects of obesity remains to be determined.

Other studies have noted similar findings in that the adenotonsillectomy is not universally curative. The percentage of patients with normal AHI postoperatively varies from 27 to 90%. This variance is in part related to the definition used for OSA, i.e., AHI/RDI and the patient population being investigated.20

In patients with obesity (Body Mass Index > 95%) the incidence of OSA can be as high as 40%. Mitchell and Kelly noted in a group of 30 obese children with pre- and postsurgical polysomnograms that the polysomnogram indices improved, but the vast majority of patients still had by definition OSA.21

These findings have been substantiated in single-center studies and literature reviews/meta-analysis. That is, adenotonsillectomy reduces the severity of OSA in children but is rarely curative.22–24

In summary, OSA in children is different from adults. Though the most common cause in pediatric patients is adenotonsillar hypertrophy, adenotonsillectomy is not always curative but greatly improves the patient’s symptoms. Whether it can influence the effects of obesity remains to be determined.

REFERENCES

Table 1. Childhood versus adult obstructive sleep apnea syndrome features

<table>
<thead>
<tr>
<th>Event</th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>2-6 yr peak</td>
<td>Increased elderly</td>
</tr>
<tr>
<td>Gender</td>
<td>Male = female</td>
<td>Males &gt; females</td>
</tr>
<tr>
<td>Obesity</td>
<td>Few</td>
<td>Most</td>
</tr>
<tr>
<td>Tonsils and adenoids</td>
<td>Often enlarged</td>
<td>Rarely enlarged</td>
</tr>
<tr>
<td>Daytime sleepiness</td>
<td>Less common than in adults but can be seen</td>
<td>Common</td>
</tr>
<tr>
<td>Obstruction</td>
<td>Obstructive apnea or hypoventilation</td>
<td>Obstructive apnea</td>
</tr>
<tr>
<td>Sleep architecture</td>
<td>Usually normal</td>
<td>Decreased delta and REM</td>
</tr>
<tr>
<td>Arousals with obstruction</td>
<td>May not be seen</td>
<td>At end of each apnea</td>
</tr>
<tr>
<td>Treatment</td>
<td>Definitive therapy in most patients</td>
<td>Selected patients</td>
</tr>
<tr>
<td>Surgical (Positive airway pressure)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


REM = rapid eye movement (Schwengel et al: Anesth Analg 109:60, 2009)

Table 2. Respiratory events that can be seen during polysomnography

<table>
<thead>
<tr>
<th>Event</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central apnea</td>
<td>Pause in airflow with absent respiratory effort, scored with &gt;20 s or 2 missed breaths and a &gt;3% drop in oxygen saturation</td>
</tr>
<tr>
<td>Obstructive apnea</td>
<td>&gt;90% reduction of airflow despite continuing respiratory effort, scored when event lasts at least 2 missed breaths in children.</td>
</tr>
<tr>
<td>Obstructive hypopnea</td>
<td>&gt;50% reduction of airflow with associated respiratory effort, scored when at least 2 missed breaths and &gt;3% drop in oxygen saturation or arousal</td>
</tr>
<tr>
<td>Mixed apneas</td>
<td>≥90% reduction in airflow, lasting at least 2 missed breaths, and containing absent respiratory effort initially (a central apneic pause), followed by resumption of respiratory effort without a resumption of airflow (an obstructive apnea).</td>
</tr>
<tr>
<td>Obstructive hypoventilation</td>
<td>End-tidal CO₂ &gt;50 mmHg for &gt;25% of the total sleep time with paradoxical respirations, snoring, and no baseline lung disease.</td>
</tr>
</tbody>
</table>


Table 3. Some congenital and medical conditions associated with obstructive sleep apnea syndrome

<table>
<thead>
<tr>
<th>Condition</th>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achondroplasia</td>
<td>Mucopolysaccharidosis</td>
</tr>
<tr>
<td>Apert syndrome</td>
<td>Obesity</td>
</tr>
<tr>
<td>Beckwith-Wiedemann syndrome</td>
<td>Osteopetrosis</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>Papillomatosis (oropharyngial)</td>
</tr>
<tr>
<td>Choanal stenosis</td>
<td>Pierre Robin syndrome</td>
</tr>
<tr>
<td>Cleft palate patients after repair</td>
<td>Pfeiffer syndrome</td>
</tr>
<tr>
<td>Crouzon syndrome</td>
<td>Pharyngeal flap surgery</td>
</tr>
<tr>
<td>Cystic hygroma</td>
<td>Prader-Willi syndrome</td>
</tr>
<tr>
<td>Down Syndrome</td>
<td>Sickie cell disease</td>
</tr>
<tr>
<td>Hallermann-Streiff syndrome</td>
<td>Treacher-Collins syndrome</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td></td>
</tr>
<tr>
<td>Klipel-Feil syndrome</td>
<td></td>
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</tbody>
</table>

13. Dsida R, Coté CJ. Nonsteroidal antiinflammatory drugs and hemorrhage following tonsillectomy: do we have the data? Anesthesiology 2004;100:749–51; author reply 751–2
Popular Misunderstandings in Neuroanesthesia

John C. Drummond, MD, FRCPC

PERSPECTIVE
I have committed considerable professional time to anesthesia for neurologic surgery. That commitment has caused me to hear a great deal related to neuroanesthesia. I have been asked by faculty colleagues in anesthesia, “What do you suppose might have gone wrong during that case yesterday?” I have listened to American Board of Anesthesiology oral examination candidates misapplying or frankly misunderstanding fundamental principles. I have been involved in third-party scrutiny of procedures that were perceived to have gone astray. I acknowledge that those interactions inform the selection of topics that follows (rather than “evidence-based” material from the peer-reviewed literature). Not all of the topics will be addressed during the course of the presentation.

THE LOWER LIMIT OF CBF AUTOREGULATION
Diagrams that appear in standard texts have frequently depicted the lower limit of human cerebral blood flow (CBF) autoregulation (LLA) as being a mean arterial blood pressure (MAP) of 50 mmHg. While this number may in fact be a reasonable representation of the LLA in several animal species, it is unlikely to be an accurate value in adult humans. The first rendering of a CBF autoregulation curve was probably that drawn by Lassen.1 His diagram depicted a LLA that might be easily interpreted to be 50 mmHg. On close inspection, however, the inflection point is probably 60 mmHg. However, the inflection point on that hand-drawn curve (wherever it is) is anchored by only 2 CBF values, both of which were obtained in pregnant females at term in whom arterial blood pressure was decreased using cerebral-vasodilating drugs and in whom baseline pressures were probably well below the population average for normal adult humans. Furthermore, numerous subsequent investigations2 (Drummond3 for additional references) suggest that the LLA in nonanesthetized adult humans is nothing less than 70 mmHg. However, it should be acknowledged that the “rules” might be different during general anesthesia for at least 2 reasons. The first is the frequent inclusion of vasodilating substances in anesthetic recipes. Vasodilators might serve to shift the autoregulation curve in a leftward direction. The second resides in the observation that sympathetomy in both experimental animals and humans during hypotension increases CBF.4 This suggests that the normal autonomic response to hypotension includes some vasoconstriction of large extracranial and perhaps intracranial vessels thereby producing effective right shifting of the autoregulation curve. If a general anesthetic were to effectively prevent that autonomic response, it is possible that some resultant left shifting of the curve might occur.

The reality, however, is that there has been exceptionally little systematic study of normal (noncerebrally injured) adult human cerebral autoregulation during anesthesia. The only context in which extensive study has occurred is during cardiopulmonary bypass (typically involving hypothermia, nonpulsatile flow, relative anemia and high-dose narcotic anesthesia). In those circumstances, which are very poorly representative of the physiology that prevails during the majority of general anesthetic states, the LLA is in fact about 65 mmHg (with a very large confidence interval indicating considerable interindividual heterogeneity).5 However, it seems inappropriate to extrapolate that average value (obtained in the context of nonpulsatile flow, low hematocrit and well maintained cardiac output) to all other anesthetic circumstances. In fact, it further seems likely that what pertains to any one anesthetic circumstance, e.g., spontaneous ventilation during anesthesia with a volatile drug, might not be relevant in another, e.g. total IV anesthetic with remifentanil and propofol. We know very little about the LLA during general anesthesia in humans and conservative assumptions should be made in the absence of more detailed knowledge.

THE PHYSIOLOGIC CENTRAL NERVOUS SYSTEM BLOOD FLOW RESERVE
Many clinicians may well respond to the preceding discussion of the LLA with their own observation that numerous patients in the span of their experience have tolerated MAPs in the 40s, 50s and 60s, i.e., well below the proposed LLA of 70 mmHg. That is inevitably true. Patients tolerate arterial blood pressures below the LLA because there is a substantial central nervous system (CNS) blood flow reserve. CNS flow can decrease by approximately 40% of baseline values before symptoms of ischemia begin to occur.6–8 That reserve is, in essence, a physiologic buffer that protects patients in the event of hypotension. However, it is important that clinicians recognize the situations in which that buffer may not be present, often because it has been encroached upon by some preexisting pathologic process. The most common situations in which the buffer is likely to have been attenuated occur in circumstances in which CNS tissue is under increased pressure. This may occur in the circumstances of increased intracranial pressure (ICP), increased ocular pressure or when CNS tissue is under extrinsic pressure, e.g., compressed under retractors or by a bulging disc. The significance of these situations is that the principal determinant of flow to the tissue is “transmural pressure” rather than blood pressure. Transmural pressure (which is commonly but probably erroneously referred to as “perfusion pressure” equals MAP minus local tissue pressure. Among the most commonly overlooked situations in which tissue pressure is increased (and the effective perfusing pressure is therefore less for a given value of MAP) is in the circumstances of spinal stenosis, in particular cervical spinal stenosis. In that group of patients, the normally wide latitudes for intraoperative blood pressure that anesthesiologists commonly allow should be tightly

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restricted. It is our approach at the University of California San Diego to maintain MAPs during anesthesia in these patients (at least until the decompression is complete) very close to normal waking levels. The drug we use most commonly to achieve this is phenylephrine. This introduces another common misconception, which is addressed in the second paragraph below.

**THE EFFECT OF HYDROSTATIC GRADIENTS ON CEREBRAL PERFUSION PRESSURE**

In patients who undergo anesthesia in horizontal positions (supine, prone, lateral), it is standard to measure arterial blood pressure with cuffs or transducers at the level of the heart. When positions are used that result in a vertical height difference between the height of the heart and the head, a pressure differential between the two that is equivalent to the weight of a column of blood of that height can be expected to occur. That gradient will be equal to approximately 2 mmHg for each one inch of height difference. The standard teaching in neuroanesthesia has long been that arterial blood pressure should be transduced at (or an arithmetic correction imposed to correct to) the level of the external auditory meatus (EAM). Clinicians who are unfamiliar with the use of the sitting position have occasionally failed to make this correction in transducer height, or have raised it only to the level of the heart with sometimes severe adverse consequences for the perfusion of the brain and/or the cervical spinal cord. This issue has been popularized recently in the context of injuries occurring in the so called “beach- chair position.” A minority have disputed this notion, arguing that a siphon-like mechanism maintains CBF in spite of reductions in cerebral perfusion pressure calculated in the manner above. Unless and until there is wider proof of that concept, conventional hydrostatic gradient concepts should apply, and arterial transducers should be raised to the level of the EAM or arithmetic corrects should be applied to cuff pressures in order to “think” in terms of blood pressure at the EAM.

**ALPHA 1 AGONISTS AND CEREBRAL VASOCONSTRICTION**

It is often asserted that the various alpha1 agonists are significant CNS vasoconstrictors. While that may be so in canines, it is not true in humans. See Miller’s Anesthesia, 6th Ed., Ch. 21, p 818 for references. (The references were regretfully omitted in the corresponding section in the 7th edition – Ch. 13, p 311.) In human investigations done many years ago, alpha one agonists were infused directly into the cerebral circulation in concentrations sufficient to produce substantial increases in systemic arterial blood pressures; and no changes in CBF were observed. The concern that phenylephrine is a CNS vasoconstrictor has too often restricted its use in situations where there was a pressing need to augment cerebral perfusion pressure. Clinicians should “get it out of their heads.” Phenylephrine is not a significant CNS vasoconstrictor in the doses that we commonly use. When arterial blood pressure support is warranted in patients who have sustained subarachnoid hemorrhage (SAH) or traumatic brain injury or when CNS structures are under compression (spinal stenosis, retractor pressure), after assuring appropriate volume status and depth of anesthesia, phenylephrine is a reasonable choice!

**THE EFFECT OF VOLATILE ANESTHETICS ON CBF**

Figures that appear widely in standard texts indicate that the common volatile anesthetics (isoflurane, sevoflurane and desflurane) cause little or no increase in CBF at sub- minimum alveolar concentrations (MAC). In the majority of elective neurosurgical patients that is almost certainly true. In fact, in subjects with generally normal cerebral physiology, CBF actually decreases from the awake state to reach a nadir in the vicinity of 0.75–1.0 MAC. Thereafter, CBF increases in parallel with increasing end-tidal concentrations of volatile anesthetics. This superficially unusual biphasic pattern is almost certainly the product of the very substantial suppression of cerebral metabolic rate (CMR) that occurs with the initial exposure to volatile anesthetics. The reduction in CBF is probably largely a “coupled” reduction in the CBF recurring as a consequence of the reduction of CMR. The important issue for clinicians is that in patients in whom CMR has already been depressed by either pathologic processes or CMR-suppressing drugs (benzodiazepines, narcotics, propofol) or who have sufficiently disordered physiology that the coupling mechanism may not be functional, volatile anesthetics may act as potent vasodilators even at the sub-MAC concentrations that are normally associated with a reduction in CBF. The consequence for the clinician is that in patients with badly impaired intracranial compliance (or, as some would say, “elastance”) especially in whom those in whom CMR is already depressed, volatile agents should be introduced very cautiously. Ideally, in those extreme circumstances, they should probably not be introduced unless ICP is being monitored or until the cranium is open and the brain can be observed directly.

**OBSURCTION OF VENOUS DRAINAGE**

The venous side of the cerebral circulation is a passive, but relatively large intracerebral compartment. It is quite commonly the cause of increased ICP or “tightness” in the surgical field and is relatively under-recognized. The cerebral venous drainage is easily obstructed by anything that puts pressure on the underlying jugular veins including circumferential ties and cervical collars. Extremes of head position can also obstruct venous drainage. Any rotation of the head that is sufficient to put tension on the sternocleido-mastoid muscles is sufficient to compress the underlying jugular vein. In addition, the jugular veins drain downstream into the chest. Accordingly, anything that increases intrathoracic pressure can impair cerebral venous drainage. This includes a medley of common entities including coughing against an endotracheal tube, kinking of the endotracheal tube, bronchospasm, and pneumothorax. Confirmation of the patency of the jugular venous system and verification of normal airway pressures are accomplished easily and should be the first things that the clinician does when evaluating increased ICP or a tight surgical field.

**HYPERVENTILATION**

It has become a well-established concept that the vasoconstriction associated with hyperventilation has the potential
to cause sufficient cerebral vasoconstriction to result in ischemia when imposed on the low-flow circumstances that can prevail after acute cerebral injuries, in particular head injury and SAH. Routine hyperventilation in neuroanesthesia and neurosurgical critical care has ceased. While prophylactic hyperventilation is never appropriate, hyperventilation is by no means totally “verboten.” Hyperventilation remains an adjunct in the management of patients with critically increased ICP at risk of herniation in whom other measures, short of barbiturate coma, have proven inadequate. Its use should be as brief as allowed for by patient circumstances.

**TENSION PNEUMOCEPHALUS**

Tension pneumocephalus is a phenomenon that can occur when gas is trapped within the intracranial space with no communication to the outside atmosphere. The phenomenon is widely associated with the sitting position and many clinicians associate its occurrence with the use of N₂O. It most certainly is a phenomenon that can be both caused or exaggerated by N₂O and many clinicians will have decided to omit N₂O from the anesthetics used for posterior fossa procedures done in the sitting position as a result. However, the assumption that one no longer needs to be concerned about tension pneumocephalus if one has made the decision to omit N₂O is an erroneous one. Clinically significant, and even life-threatening, tension pneumocephalus can occur in the absence of the use of N₂O. Imagine a situation in which a craniotomy has been performed in a head-up posture with the craniotomy located such that a significant portion of the cranium is above the surgical site. With optimal venous drainage, mannitol administration, hyperventilation, the use of anesthetic drugs that reduce brain bulk and opening of the arachnoid membrane resulting in drainage of cerebrospinal fluid, a substantial potential space can occur between the surface of brain parenchyma and the highest point of the skull. That space will fill with air. When the procedure is concluded and the patient is restored to a near supine position, venous blood, arterial blood, cerebrospinal fluid and extracellular fluid all begin to return. Albeit that the oxygen is absorbed quickly from the air within the cranium, the remaining nitrogen can be a substantial and unyielding “mass” that will diffuse away only very slowly (over a period of days). Frontal craniotomies performed in a brow-up position in which the frontal bone is removed and replaced, are particularly prone to the development of tension pneumocephalus in the immediate postoperative period. Tension pneumocephalus is an under-appreciated and under-recognized cause of postoperative delayed awakening, delirium and nonawakening. When it is suspected, the diagnosis can be made by a cross table lateral radiograph or, more commonly in these days, readily available computed tomography. The treatment entails a twist drill hole and dural perforation, ideally performed by the surgeon.

**THE BRAIN PARENCHYMA IS INSENSATE BUT THE CRANIAL NERVES ARE NOT**

When Wilder Penfield performed the brain surface stimulation surveys that lead to the development of the now familiar homunculus diagrams, the craniotomies were performed under local anesthesia. While the meninges have some innervation and required gentle handling and some local anesthesia at the skull base, brain stimulation and/or resection of brain parenchyma required no anesthesia whatsoever. The brain parenchyma is insensate. Accordingly, when a general anesthetic is used for intracranial neurosurgery, the intracranial portion requires only “light” anesthesia. An error occasionally made by clinicians is the failure to anticipate stimulation of the extra-axial but intracranial portion of cranial nerves. The issue arises most often in the context of procedures formed in the vicinity of the fifth cranial nerve. The fifth cranial nerve suberves the sensation from the entire face and mouth. Stimulation of the extra-axial portion of the fifth cranial nerve can result in very sudden arousal. In circumstances in which this has occurred in nonparalyzed patients, the arousal has resulted in sudden straining against the endotracheal tube with herniation of brain around retractors and around the edges of the bony craniotomy. Substantial injury to brain parenchyma and adverse neurologic events have occurred. Where feasible, patients should be maintained paralyzed during surgery in this vicinity of Cranial Nerve V. When patients are not paralyzed, clinicians should be very attentive to the possibility of arousal and should be ready to deepen anesthesia at a second’s notice, e.g., a syringe of induction drug should be maintained in line at all times.

**STRIDOR/NARROW AIRWAY**

Swelling and expanding hematomas occurring after carotid endarterectomy or anterior cervical discectomy/fusion procedures have the potential to encroach upon the extra-thoracic airway. The clinician should keep several principles in mind. 1) The airway will always look much worse on the inside than it does on the outside. Swelling of periglottic structures is a larger component of airway compromise than is mechanical encroachment. I suspect that the enlarging mass impairs lymphpatic and venous drainage. When one visualizes in the airway, there is often remarkable swelling of periglottic structures. 2) Stridor is a late (and ominous sign). Delaying in the face of progressive enlargement of the neck until stridor occurs increases the likelihood of extreme difficulty in securing the airway. 3) Racemic epinephrine (or Heliox) may “buy you time” in the event of respiratory compromise, but they should not be viewed as cures. When an airway has become sufficiently narrow to produce stridor and labored respiration (and concomitant turbulent flow), very small increases in airway diameter will reduce airway resistance enough to mitigate symptoms. But the clinician should assume that progressive swelling will occur if the mass lesion is not relieved and distress will recur.

**REFERENCES**

3. Drummond JC. The lower limit of autoregulation: time to revise our thinking? Anesthesiology 1997;86:1431–3


10. Drummond JC, Hargens AR, Patel PM. Hydrostatic gradient is important - Blood pressure should be corrected. Anesthesia Patient Safety Foundation Newsletter 2009;24:6


Rapid Recovery from Ambulatory Surgery: The New Paradigm in Ambulatory Anesthesia

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INTRODUCTION
Ambulatory surgery continues to expand with complex patients having several comorbid conditions undergoing complex and invasive surgical procedures. Simultaneously, there is emphasis on enhanced postoperative recovery that has been shown to facilitate early discharge home and early resumption of normal daily activities. The process of enhanced recovery starts preoperatively and continues until the patient returns to activities of daily living. It involves preoperative optimization of patients’ health, use of anesthetic techniques that optimize surgical conditions while ensuring rapid recovery with minimal side effects, prevention of common postoperative complications, and aggressive rehabilitation with the aim of restoring the patient to the best health possible. This requires a multidisciplinary approach to perioperative care in which the anesthesiologist can play a lead role. The aim of this presentation is to discuss the current evidence for optimal perioperative care that would allow rapid recovery after ambulatory surgery in adults.

PREOPERATIVE ASSESSMENT AND OPTIMIZATION
Preoperative assessment and optimization of comorbid conditions is associated with improved perioperative outcome. Also, this avoids delays and cancellations on the day of surgery. Similarly, appropriate patient selection is critical for reducing perioperative complications and improving outcome. Patient selection for ambulatory surgery depends upon several factors including patient-related factors (i.e., presence and severity of coexisting comorbidities), surgery-related factors (i.e., invasiveness of surgery and surgeon’s experience), anesthesia-related factors (i.e., type of anesthesia), and venue-related factors (i.e., hospital-based ambulatory surgery, free-standing ambulatory surgery center with or without overnight stay, and office settings).

ANESTHETIC TECHNIQUES FOR RAPID RECOVERY
An ideal anesthetic technique should provide smooth and rapid onset, optimal operating conditions, and rapid recovery, with minimal (if any) side effects. The choice of anesthetic technique (i.e., general versus regional anesthesia) is an important determinant of recovery after ambulatory surgery. Use of local anesthetic techniques including peripheral nerve blocks with or without sedation/analgesia allows rapid recovery, reduces time to home readiness, provides postoperative analgesia, and reduces opioid requirements. However, use of spinal anesthesia may prolong the postesthesia care unit (PACU) stay as well as delay ambulation and time to home-readiness. Therefore, while the role of local/peripheral nerve blocks is increasing, the role of spinal anesthesia in ambulatory surgery is diminishing.

There is a lack of evidence regarding superiority of a specific general anesthetic technique (e.g., inhaled versus total IV anesthesia [TIVA]) with respect to discharge home after ambulatory surgery. The benefits of TIVA include the ability to provide general anesthesia without the need for an anesthesia machine. On the other hand, inhaled anesthetics exert some neuromuscular blocking effect, which may reduce the need for muscle relaxants and the potential for residual muscle paralysis.

It is necessary to avoid deep anesthesia, as it may delay emergence from anesthesia. Because different types of surgical stimuli (e.g., skin versus intracavity incisions) result in different degrees of hemodynamic response, the anesthetic and analgesic requirements may vary at different stages of the surgical procedure. However, determining the optimal anesthetic concentrations that would parallel the varying surgical stimuli, while preventing intraoperative awareness, remains challenging. Recent evidence suggests that titration of inhaled anesthetics using end-tidal concentrations (0.7–1.3 minimum alveolar concentration [MAC] values) and propofol TIVA using Bispectral Index monitoring should prevent intraoperative awareness with recall.

Airway Management
Supralaryngeal devices (e.g., laryngeal mask airway) have gained widespread popularity as general-purpose airway devices and are increasingly used for routine elective surgical procedures. Compared with the tracheal tube, these devices do not require muscle relaxation and laryngoscopy, and thus may prevent complications associated with tracheal intubation. These devices are tolerated at lower anesthetic concentrations than the tracheal tube and therefore allow titration of anesthetic concentrations to the surgical stimulus. With the patient breathing spontaneously, opioid requirements can be based on the respiratory rate while dosing requirements of sedative-hypnotic anesthetics can be titrated to end-tidal concentrations of inhaled anesthetics or brain function monitor. This may allow for an earlier emergence from anesthesia and improve perioperative efficiency. Although the safety of supralaryngeal devices in healthy patients has been established, their use in patients at high risk of regurgitation of gastric contents (e.g., gastroesophageal reflux disease, morbid obesity, laparoscopy, and lithotomy/prone position) remains controversies.

Inhaled Anesthetics
The choice of inhaled anesthetics (i.e., desflurane versus sevoflurane) remains controversial. Although clinical differences between desflurane and sevoflurane, with respect to...
time to home readiness, appear to be small, several studies have reported more rapid emergence from anesthesia with desflurane. A study analyzing data from published randomized trials as well as data from an electronic database found that desflurane reduced the average tracheal extubation time and the variability of extubation time compared with sevoflurane.

Nitrous Oxide
Because of its amnestic and analgesic properties, nitrous oxide (N\textsubscript{2}O) can reduce the requirements of anesthetic and analgesic drugs. However, the routine use of N\textsubscript{2}O is questioned due to concerns of increased incidences of postoperative nausea and vomiting (PONV) and pressure effects through expansion of closed spaces.10 However, the clinical significance of these side effects in modern anesthetic practice has been questioned.11 A systematic review assessing the emetic effects of N\textsubscript{2}O found that the overall impact of avoiding N\textsubscript{2}O on the incidence of PONV was modest (absolute 33% vs. 27%).12 In addition, propofol induction and use of prophylactic antiemetics, which is the current standard of care for ambulatory surgery, may further negate the emetic effects of N\textsubscript{2}O.12

Another benefit of N\textsubscript{2}O is that it facilitates the removal of other inhaled anesthetics (i.e., second gas effect), and allows rapid emergence from anesthesia.13 Furthermore, the analgesic effects of N\textsubscript{2}O should reduce the need for intraoperative opioids and reduce opioid-related adverse effects. Of note, N\textsubscript{2}O has been shown to reduce opioid-induced hyperalgesia14 as well as reduce the incidence and severity of persistent postoperative pain.15 Interestingly, a recent propensity-matched observational trial reported that N\textsubscript{2}O reduced perioperative morbidity and mortality.15 A systematic review found that omission of N\textsubscript{2}O significantly increased the risk of awareness.16

Overall, N\textsubscript{2}O can improve the quality and safety of induction and maintenance of general anesthesia as well as facilitate recovery with clinically insignificant adverse effects. Thus, there is no convincing reason to avoid N\textsubscript{2}O.

Muscle Relaxants and Reversal of Residual Neuromuscular Blockade
Several studies have demonstrated that many patients return to the PACU with residual paralysis, defined as a train-of-four (TOF) ratio of <0.9, despite the signs of clinical recovery from neuromuscular blockade.17-19 Residual paralysis can increase the incidence of critical respiratory events in the PACU and prolong recovery time as well as increase postoperative morbidity and mortality.20,21 Residual paralysis may be particularly detrimental in patients with morbid obesity, sleep apnea and significant pulmonary disease.

The first step in reducing the incidence of residual paralysis is to use the smallest possible dose of muscle relaxant that will provide optimal surgical conditions, rather than to maintain a certain TOF count (e.g., one twitch of the TOF response). Because the clinical indicators currently used to detect return of neuromuscular function are not sensitive or specific and the TOF response has limited value at deeper levels of neuromuscular blockade, it is difficult to recognize residual paralysis in clinical practice.17-19 Nevertheless, anesthesia practitioners judge themselves as better skilled at avoiding residual paralysis than they do their colleagues, making them overconfident in their capacity to estimate recovery of neuromuscular function.22 Therefore, general opinion favors administration of an anticholinesterase inhibitor at the end of anesthesia unless quantitative methods of evaluation of neuromuscular function (e.g., acceleromyography) suggest adequate recovery (i.e., TOF ratio >0.9).

The questions commonly faced at the time of reversal include, should all patients receive a reversal? If so, should we always use a “full” dose of reversal? If not, what is the optimal dose of neostigmine? What is the optimal dose of glycopyrrolate?

Uwarranted administration of neostigmine (i.e., administration after recovery of the TOF ratio >0.9) can result in paralysis suggesting that neostigmine itself may have muscle-relaxant properties.23 Therefore, routine administration of a full dose of neostigmine may not be appropriate. Current evidence suggests that the dose of anticholinesterase inhibitor should be titrated to the intensity of neuromuscular blockade at the time of reversal.24 Importantly, TOF monitoring of the ulnar nerve at the wrist, rather than the eye muscles, should be used to determine the dose of neostigmine. A recent study has shown that patients having TOF monitoring of the eye muscles had a more than 5-fold higher risk of postoperative residual paralysis than those who had monitoring of the adductor pollicis.25 Of note, the ratio of neostigmine and glycopyrrolate should be 1:1 (by volume), in most cases.

Adherence to evidence-based practices related to neuromuscular blockade dosing, monitoring, and reversal has been shown to improve patient outcomes during the early recovery period.

PERIPHERAL NERVE STIMULATOR ASSESSMENT AT THE ULNAR NERVE

1. TOF count 4, with no fade - administer neostigmine 20 mcg/kg, ideal body weight
2. TOF count 4, with fade - administer neostigmine 30 mcg/kg, ideal body weight
3. TOF count 3 - administer neostigmine 40 mcg/kg, ideal body weight
4. TOF count 2 - administer neostigmine 50 mcg/kg, ideal body weight
5. TOF count 1 - administer neostigmine 60 mcg/kg, ideal body weight
6. No TOF response - delay reversal.

Intraoperative Antinociception
The sympathetic stimulation and hemodynamic responses from noxious surgical stimuli may be reduced by using N\textsubscript{2}O, opioids, and non-opioid analgesics (i.e., the analgesic component). Opioids provide intraoperative analgesia, hemodynamic stability, and reduce requirements for hypnotic/sedatives. During induction of general anesthesia, laryngoscopy and tracheal intubation constitute profound noxious stimuli. Therefore, an opioid analgesic is commonly administered concomitantly with an IV hypnotic/sedative (e.g., propofol) to provide clinically acceptable hemodynamic control. Also, opioids reduce anesthetic requirements.26,27 However, quantification of the drug
interaction (i.e., additive or synergistic) is difficult. There
appears to be a “ceiling effect” of opioids in anesthetic
interactions, as opioids do not reduce the MAC values of
inhaled anesthetics by more than two-thirds.26,27

The questions commonly faced with respect to intraop-
erative opioid use include, what is the optimal opioid choice
and dose at the time of induction of anesthesia. Also, what
is the optimal opioid choice and dose in the intraoperative
period? What is the optimal opioid choice and dose at the
end of surgery that would provide optimal analgesia at the
time of emergence without causing respiratory depression
and delaying tracheal extubation?

The choice of intraoperative opioid is often based on
empirical judgment. A rational opioid selection and dos-
ing should contribute to rapid recovery after anesthesia.
Fentanyl is the most commonly used opioid for intra-
operative analgesia. Sufentanil, a fentanyl analog, is
approximately 10 times more potent than fentanyl with a
similar onset of action. In contrast to fentanyl, the context-
sensitive half-time of sufentanil is significantly shorter.
Remifentanil has unique pharmacokinetics and ultra-short
duration that allows optimal matching of the dose with
the varying degree of surgical stimuli at different stages
of surgery. In addition, the short and predictable duration
of remifentanil make it suitable in the high-risk popula-
tion such as the elderly, morbidly obese, and those with
obstructive sleep apnea. However, there appears to be a
learning curve with the use of remifentanil.28 Optimal
dosing of remifentanil would include avoidance of bolus
dosing and an initial infusion rate of 0.25 \( \mu g/\)kg/min.29 A
recent study found that remifentanil 0.5 \( \mu g/\)kg caused
similar ventilatory depression as fentanyl 1 \( mcg/\)kg.30
Because of its rapid offset of analgesic effect, it is neces-
sary that a longer-acting opioid or non-opioid analgesic
be used to provide postoperative analgesia. The benefits
of remifentanil may be realized if a non-opioid analgesic
technique can be used.

Optimal opioid dosing at the time of induction and dur-
ing maintenance of anesthesia remains controversial. It is
common practice to use relatively larger opioid doses at
induction of anesthesia (“front loading”), particularly in
longer surgical procedures. However, the validity of this
approach is questionable. Larger opioid doses may result
in significant postinduction hypotension and need for phar-
macological support. Also, this may increase the potential
for acute tolerance as well as delayed hyperalgesia, which
may increase the degree of postoperative pain.31 Higher
intraoperative opioid doses may increase opioid-related
side effects including nausea, vomiting, sedation, bladder
dysfunction, and respiratory depression.

The need for intraoperative opioids is commonly based
on hemodynamics (heart rate and arterial blood pressure).
However, attempts to achieve “tight” hemodynamic control
may result in use of larger opioid doses. Because intraopera-
tive opioid overdose can only be recognized at emergence
from anesthesia when the patient’s spontaneous ventilation
is delayed, it is imperative that opioids are administered
judiciously. In addition, the use of non-opioid analgesics to
reduce the opioid-related side effects may minimize postop-
erative complications and expedite recovery.

As a plan for postoperative analgesia, it is common prac-
tice to administer a long-acting opioid towards the end of
surgery. The choice of long-acting opioid includes morphine
and hydromorphone of which hydromorphone is prefer-
dable due to its superior pharmacokinetics.32 Compared with
morphine, hydromorphone has a shorter plasma-central
nervous effect-site equilibration half-life. Hydromorphone
has a quicker onset time and the concentrations at the effect-
site do not increase after titration has stopped.32 Therefore,
hydromorphone may be better suited than morphine for
titration of acute pain. Morphine is poorly suited by titra-
tion for immediate analgesia, as delayed respiratory depres-
sion may result due to the slow transfer of morphine to the
effect site.

The dosing for hydromorphone could be based on the
studies of morphine. Morphine (2–3 mg every 5–10 min)
titrated to achieve a respiratory rate of 12–15 breaths per
minute during emergence from anesthesia can enhance postoperative analgesia and reduce PACU stay without
increasing the incidence of respiratory depression.33 The
total dose of morphine usually required is 0.15 mg/kg. This
dose usually does not delay awakening or delay tracheal
extubation.33

Intraoperative Mechanical Ventilation
Optimal intraoperative ventilatory strategy would
include use of lower tidal volume (6–8 ml/kg, ideal
body weight) with positive end-expiratory pressure.34 It
is important to avoid hyperventilation as it may result in
metabolic alkalosis and lead to postoperative hypoventi-
lation. Most importantly, it is recommended that the end-
tidal carbon dioxide (CO₂) levels be maintained around 40
mmHg rather than the traditional values of 30–35 mmHg.
Higher CO₂ levels improve hemodynamics and improve
tissue perfusion.

EMERGENCE FROM GENERAL ANESTHESIA
Towards the end of surgery, it is common practice to reduce
the respiratory rate in an effort to build up end-tidal CO₂
levels and facilitate respiration. However, the reduced
minute ventilation resulting from this practice may delay
removal of inhaled anesthetic, and thus delay emergence
from anesthesia. Therefore, the primary aim at the end of
the surgery should be to maintain the minute ventilation
in an effort to washout the inhaled anesthetic and facilitate
emergence.35 One of the major concerns during emergence
from anesthesia, particularly in obese and sleep apnea
patients, is the risk of airway obstruction after tracheal
extubation. Rapid emergence from anesthesia should
prevent this complication.

PREVENTION OF POSTOPERATIVE
COMPLICATIONS
One of the major goals of an ideal anesthetic technique is
prevention of postoperative complications particularly
pain, nausea, and vomiting. The other postoperative com-
lications that can impede recovery include cardiovascu-
lar alteration (i.e., hypotension, hypertension, and rhythm
disturbances), respiratory complications (i.e., airway
obstruction, hypoventilation, brochospasm, and pulmonary
aspiration), temperature abnormalities, and surgical complications.

Postoperative Pain Management
The goal of pain management should be to minimize pain not only at rest, but also during mobilization and physical therapy. An ideal approach to optimal pain management starts with patient education, as it reduces anxiety, allows realistic expectation, and improves patient satisfaction. Procedure-specific, evidence-based analgesic techniques that are incorporated in a clinical pathway have the highest chances of being implemented consistently.36,37

Since the introduction of the IV formulation of acetaminophen, it has been increasingly used as a part of multimodal analgesia.38 An optimal multimodal analgesia technique would include acetaminophen combined with nonsteroidal antiinflammatory drugs (NSAIDs) or cyclooxygenase (COX)-2 specific inhibitors. The combination of acetaminophen and NSAIDs or COX-2 specific inhibitors has been shown to provide superior analgesia compared with either drug alone.39,40 The analgesic efficacy of COX-2 specific inhibitors is similar to that of the traditional NSAIDs. Because the COX-2 specific inhibitors spare the COX-1 enzyme, they do not have any antiplatelet effects. Thus, they can be administered preoperatively, as there is no concern of increased perioperative bleeding. However, in the perioperative period, the cardiovascular and renal adverse effect profile of COX-2 specific inhibitors seems to be equivalent to that of traditional NSAIDs. Of note, acetaminophen exhibits an analgesic ceiling effect similar to NSAIDs and COX-2 specific inhibitors.41

Infiltration of the surgical wound with local anesthetic can provide excellent analgesia that outlasts the duration of action of the drug and is recommended for routine use. Local anesthetic techniques provide pain relief until the onset of oral analgesics. The duration of analgesia can be increased by infusion of local anesthetics through a catheter placed in the layers of the skin. A new formulation of bupivacaine using liposomal technology which is reported to have a duration of up to 72 h has been recently been introduced into clinical practice. This may obviate the need for using continuous wound local anesthetic infusion. In addition, peripheral nerve blocks are increasingly being used to provide intra- and postoperative analgesia. The use of continuous perineural local anesthetic infusions after ambulatory surgery has been shown to extend the duration of analgesia and allow more extensive and painful surgical procedures to be performed on an outpatient basis. However, placement of these blocks may require preoperative and postoperative logistic planning.

Several systematic reviews have reported that dexamethasone 4–8 mg, IV administered either pre- or intraoperatively provides significant pain relief and reduces opioid requirements.42,43 A single dose of dexamethasone has not been shown to increase the incidence of surgical site infections, but it may increase blood glucose levels lasting for up to 24 hours postoperatively. However, the clinical significance of this increase in blood glucose levels is not known. Low-dose ketamine has been reported to reduce postoperative pain scores and opioid consumption as well as delay time to first opioid administration. A recent systematic review revealed that ketamine provided significant analgesic benefits in painful procedures including thoracic, upper abdominal, and major orthopedic surgeries.44 Interestingly, the analgesic effects of ketamine were independent of the type of intraoperative opioid administered, timing of ketamine administration, and the ketamine dose. The authors also concluded that the opioid-sparing effect of ketamine reduced the incidence of nausea and vomiting, but was associated with an increase in the incidence of neuropsychiatric disturbances.44 However, the role of low-dose ketamine as an adjunct to other non-opioid analgesics in ambulatory surgery remains controversial, as the optimal dose and duration of administration is unknown. The role of anticonvulsants (e.g., gabapentin and pregabalin) in the outpatient setting needs to be clarified by further investigation.

These analgesics should be administered on a regular “round-the-clock” basis with opioids used as “rescue” analgesics. Opioids should be used sparingly as opioid-related adverse effects delay recovery and return to activities of daily living. Tramadol, a weak opioid agonist and a weak norepinephrine and serotonin reuptake inhibitor, is commonly used in the perioperative period. Although it is generally well tolerated, side effects include nausea, vomiting, dizziness, and drowsiness. Also, tramadol has a potential to cause seizures, and therefore should be used with caution in patients with increased intracranial pressures, epilepsy, and in patients receiving neuroleptic drugs. It is contraindicated in patients receiving monoamine oxidase inhibitors.

Postoperative Nausea and Vomiting
Postoperative nausea and vomiting (PONV) are factors that can delay recovery. Although risk-based approaches for antiemetic therapy have been proposed,45 the compliance with these strategies has been shown to be poor. Therefore, prophylactic multimodal antiemetic therapy should be used in all ambulatory surgical patients. The number of antiemetic combinations could be based on the patient’s level of risk and surgical procedure.46 A combination of dexamethasone 4–8 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 PONV, high opioid requirements for pain relief) may receive additional antiemetic therapy such as preoperative transdermal scopolamine or oral aprepitant. In addition, TIVA may be considered in these high-risk patients. Interestingly, a recent systematic review reported that metoclopramide 10 mg was effective in preventing PONV, and that it should be an alternative drug to prevent PONV.47 Patients requiring rescue antiemetic therapy in the immediate postoperative period could receive low-dose promethazine (6.25 mg, slow IV) or dimenhydrinate (1 mg/kg).

Postdischarge nausea and vomiting (PDNV) are common and are sometimes severe adverse outcomes for ambulatory patients.48 The independent predictors of PDNV include female gender, age younger than 50 years, history of PONV, opioids administered in the PACU, and nausea in the PACU. The overall incidence of PDNV can be determined by the presence of the total number of predictors.48
POSTOPERATIVE COURSE AFTER AMBULATORY SURGERY

In addition to achieving rapid emergence from anesthesia, it is necessary that the recovery process be modified to improve patient throughput. The first step is to change from traditional time-based to clinical-based discharge criteria from the PACU and the phase II unit. Use of appropriate scoring systems allows patients to be safely discharged from the PACU and to be discharged home. If the criteria used to discharge patients from the PACU were met in the operating room, it would be appropriate to consider bypassing the PACU and transferring the patient directly to the phase II unit.

A clearly defined process should be established to ensure safe and timely discharge home. Appropriate modifications of current discharge criteria based upon recent literature should allow us to discharge patients expeditiously without compromising safety. The American Society of Anesthesiologists practice guidelines recommend that the ability to tolerate oral fluids should not be part of a routine discharge protocol but may be appropriate for selected patients (e.g., likelihood of complications if fluids are not taken). Similarly, a routine requirement for voiding before discharge should not be a part of a discharge protocol and may only be necessary in selected patients (e.g., the type of surgery performed, history of urinary retention and anesthetic technique used).

A clear and coordinated postdischarge plan is necessary. Patients should be encouraged to ambulate and resume activities of daily living as early as possible. It is important to recognize that home-readiness is not synonymous with street-fitness. Therefore, patients should be given clear instructions and cautioned against performing functions that require complete recovery of cognitive ability. Although a majority of surgical care is being performed on an ambulatory basis, there is limited information regarding outcome after discharge home.

SUMMARY

It is necessary to develop comprehensive, multidisciplinary, procedure-specific clinical pathways that involve the entire perioperative team (e.g., anesthesiologists, surgeons, pharmacists, and nursing). Preoperative patient education with clear instructions sets expectations, reduces patient anxiety and increases their satisfaction. The most important aspect of a general anesthetic technique is its ability to consistently achieve rapid recovery to patients’ normal functioning after termination of surgery. Thus, it is necessary to use anesthetic, analgesic, and muscle relaxant drugs judiciously. Avoidance of residual muscle paralysis is critical. Opioid-related adverse effects may be associated with delayed recovery and thus opioids should be used judiciously, and non-opioid analgesics should be used whenever possible. Propylactic multimodal analgesia and antiemetic therapy are critical in achieving rapid recovery. Postdischarge planning should include prevention and treatment of postoperative complications particularly pain and antiemetic therapy. Perioperative outcomes (e.g., time to home readiness, time to actual discharge, unanticipated hospital admission, hospital readmission, patient satisfaction, morbidity and mortality) should be recorded.

REFERENCES

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www.iars.org IARS 2013 REVIEW COURSE LECTURES


30. Gelberg J, Jomarker C, Stenqvist O, Werner O. Intraoperative boluses of fentanyl, 1 μg kg⁻¹, and remifentanil, 0.5 μg kg⁻¹, give similar maximum ventilatory depression in awake volunteers. Br J Anaesth 2012;108:1028–24


35. Joshi GP. The role of carbon dioxide in facilitating emergence from inhalation anesthesia: then & now. Anesth Analg 2012;114:933–4


The New Organizational Vital Sign: Quality and Patient Safety

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The objectives of this review are: To define quality and describe why it is important in the current health care environment; to briefly illustrate Cleveland Clinic Quality and Patient Safety Institute infrastructure; to describe why using thresholds alone for quality metrics is not always optimal and to demonstrate practical applications of current process improvement metrics and quality initiatives from our Quality and Patient Safety Institute.

Atalden and Davidoff emphasized the inextricable link between the domains of professional development, health care delivery and patient outcomes to contribute to better outcomes for all three domains. They defined quality improvement as: “the combined and unceasing efforts of everyone—healthcare professionals, patients and their families, researchers, payers, planners and educators to make changes that will lead to better patient outcomes (health), better system performance (care) and better professional development (learning).” Implicit in their definition is their conviction that better outcomes necessitate quality improvement be integrated into all parts of a health care system.

Traditional approaches to quality assurance focused on the “tail” where thresholds were used to establish a statistical tail; the subsequent goal was to concentrate quality improvement activities on the tail region to avoid being an outlier. Brent James has described this as “threshold-based quality assurance.” The pitfall of threshold-based quality assurance is that there is a risk for thresholds to become an end in themselves; i.e., these artificial boundaries may limit institutions from further quality improvements since they are within the boundary of what is deemed ‘good enough’.

Case Example

Health care systems, governmental and accrediting agencies and payers primarily collect outcomes data from sources used for administrative purposes. In contrast, clinical data sources, which are often prospectively collected are considered superior to administrative data in the assessment of patient outcomes. This ongoing tension between administrative and clinical registries and the need for health care organizations to demonstrate accountability for the quality of care delivered necessitates a better understanding of the data sources used for public reporting. On a local level we found inconsistencies in quality events between administrative and clinical data sources. This prompted us to explore data used in the context of public reporting of quality outcomes and data used for quality improvement initiatives. Our study demonstrated considerable lack of concordance between administrative data sources and two separate sources of clinically collected data (National Surgical Quality Improvement Program and Cardiovascular Information Registry). The inconsistencies were related to a number of factors: differences in definitions among the three sources of data, sequences of outcomes documentation, coding, abstraction and data management and presentation. Our work emphasized the need for a national consensus on data definitions and for physicians to become more actively involved in understanding and using quality data.

Case Example

High performing institutions have continuous quality improvement integrated at multiple levels in their health care system. Patient safety initiatives to reduce complications and improve outcome is the goal of quality and patient safety. We reported on the morbidity complications associated with reoperation for bleeding, a complication after cardiac surgical interventions. We developed and instituted a process-improvement initiative to reduce the occurrence of this complication in our operative setting with the use of a formalized hemostasis checklist. A number of studies have reported on reductions in error with the use of formalized checklists. While common in other industries, checklists have only more recently been integrated into a number of workflow processes in health care and operative environments. After our 12-month staged checklist implementation we reported significant reductions in reoperation for bleeding events in our surgical setting.

Case Example

In multiple settings the presence of anemia is associated with increased morbidity and poor quality of life. In a large population of nontransfused cardiac surgical patients we previously reported on the prevalence of perioperative anemia and its morbidity complications. There were several predictors for low nadir hematocrit, some were potentially modifiable others were not. Within hospitalized patients the development of anemia occurring during the course of hospitalization is associated with an increased risk for both morbidity and mortality. Development of hospital-acquired anemia is multifactorial and related to factors such as procedural blood loss, phlebotomy, and blunted erythropoiesis of chronic disease. We examined the prevalence of hospital-acquired anemia, and morbidity and resource utilization in more than 400,000 hospitalizations within our health care system. We reported that anemia acquired during the course of hospitalization was common and associated with increased in-hospital mortality, length...
of stay and total charges. It appears to be a “hazard of hospitalization” that is potentially modifiable.

**CONCLUSION**

W. Edwards Deming noted “Improve constantly and forever the system of production and service, to improve quality and productivity, and thus constantly decrease costs.” A well-designed quality and patient safety infrastructure provides the tools to measure, document and continually evaluate processes-of-care within a health system. Key to this infrastructure is the development of a culture of safety. The operative setting is a particularly complex microsystem, however well designed, work processes and attention to continuous improvement and safe delivery of care ultimately benefit patient outcome. The value for patients and a health system is a high level of quality of care delivered in a safe and efficient manner.

**BIBLIOGRAPHY:**

1. Batalden PB, Davidoff F. What is “quality improvement” and how can it transform healthcare? Qual Saf Health Care 2007;16:2–3


Bispectral Index Monitoring and Perioperative Outcomes: Does It Make a Difference?

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It is hypothesized that incorporating a brain monitor, like the Bispectral Index (BIS), into routine anesthetic practice can improve anesthetic management and patient outcomes by eschewing both too little and unnecessarily deep anesthesia. By avoiding light anesthesia, intraoperative awareness and its attendant complications, like post-traumatic stress disorder, can be prevented. Evidence from several large trials suggests that a BIS-based protocol decreases intraoperative awareness with postoperative recall when total IV anesthesia with pharmacological paralysis is administered.1–3

However, when anesthesia is based on a potent volatile drug, a BIS-based protocol is not superior to a protocol based on exhaled anesthetic concentration in preventing awareness with recall (Figure 1).3–6 Unnecessarily deep anesthesia is almost certainly associated with prolonged recovery and poorer quality of recovery. More controversially, deep anesthesia has been postulated to increase directly a variety of postoperative complications, including mortality, delirium, cognitive decline, dementia, myocardial infarction, stroke, renal failure and cancer.

Some trials have indicated that a BIS-based protocol may decrease anesthetic administration and improve early recovery (discharge from postanesthesia care unit, nausea, vomiting) compared with routine care or an alternative protocol,7–9 but other trials have not replicated these findings.1,3,5 An association has been noted between the cumulative duration of low BIS and intermediate-term mortality (1–4 years);10–12 this association was independent of anesthetic duration or volatile anesthetic concentration. Other studies have not found that cumulative duration of BIS<45 in isolation was connected with increased mortality.13,14

If the link between triple low and death is causal, the pathophysiologic mechanisms by which triple low could indiscriminately increase mortality, especially cancer deaths, are unclear.15 Thus, relations between intraoperative BIS values (or other surrogate measures of anesthetic depth) and adverse postoperative outcomes (e.g., death, myocardial infarction, stroke, renal failure, cognitive decline, dementia, cancer recurrence) require scrupulous investigation.

There is mounting evidence from several randomized, controlled trials that a BIS-based protocol can decrease postoperative delirium, possibly by decreasing anesthetic administration or by minimizing epochs of electroencephalographic burst suppression.6,16,17 The results of an unpublished meta-analysis [Whitlock et al.] of four randomized studies comparing BIS-guided anesthesia with a control group (routine care or an alternative protocol) suggest that BIS-guided anesthesia lessens postoperative delirium, with a summary odds ratio of 0.56 (95% confidence interval, 0.42 to 0.73) (Figure 2).6,16–18 Although the finding is compelling, the mechanism for decreased delirium is unclear because most large studies have not demonstrated that BIS guidance alters average anesthetic administration.1–5,16 Furthermore, logic would suggest that if a slight reduction in general anesthetic administration is associated with improved clinical outcomes, the use of no general anesthesia (e.g., medical management or regional anesthesia) should result in substantially better outcomes. On the contrary, meta-analyses of trials that have randomized patients to general or regional anesthesia for surgical procedures and large effectiveness trials that have randomized patients to major surgery with deep general anesthesia versus nonsurgical management (e.g., coronary artery bypass grafting versus percutaneous stenting) have failed to demonstrate an improvement in outcomes (e.g., mortality, cognitive decline, delirium, quality of life) up to five years later with regional anesthesia or nonsurgical, nonanesthetic management.19–24 Before we can conclude that a minor decrement in anesthetic concentration (or anesthetic depth) improves outcomes, we must demonstrate that general anesthesia at any concentration is injurious to patients.

Although skepticism is important and we should not reach overly hasty inferences, there is accumulating evidence that brain monitoring helps practitioners to administer anesthesia more appropriately for some individual patients, and is therefore likely to be associated with some improvements in patient outcomes. Hence brain monitoring during general anesthesia could enjoy more widespread adoption. In the United Kingdom, for example, guidelines from the National Institute for Health and Care Excellence (NICE) recommend the use of electroencephalography-based brain monitoring, especially in vulnerable patients.25 Implementation of these guidelines has been controversial due to the lack of definitive evidence for the benefit of such monitors26 and insufficient information on what constitutes “vulnerability.” Thus, most anesthesiologists in the United Kingdom currently do not follow the NICE guidelines, and either through choice or unavailability of the devices, do not use electroencephalography-based brain monitors.27 Nonetheless, brain monitoring is heuristically appealing as the brain is the target organ of general anesthesia. The BIS is only one of many available brain monitors; while it has been an important advance and has helped focus the attention of the anesthesiology practice can improve anesthetic management and patient outcomes by eschewing both too little and unnecessarily deep anesthesia. By avoiding light anesthesia, intraoperative awareness and its attendant complications, like post-traumatic stress disorder, can be prevented. Evidence from several large trials suggests that a BIS-based protocol decreases intraoperative awareness with postoperative recall when total IV anesthesia with pharmacological paralysis is administered.1–3

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community on the brain, BIS has important limitations that must be addressed in future devices. New brain monitoring approaches rooted in principles of neurobiology are being explored and could make the administration of general anesthesia less based on gestalt and median population parameters, and more driven by measured effects on its target organ.

REFERENCES


11. Dahaba AA. Different conditions that could result in the bispectral index indicating an incorrect hypnotic state. Anesth Analg 2005;101:765–73


Is There a Link Between Acute Pain and Chronic Pain?

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Pain is a normal physiologic response to injury. The presence of pain signals impending tissue injury and signals the need to protect the injured area during healing. Under some circumstances, pain persists after all tissue has healed. We now have a detailed understanding of the physiologic mechanisms that are responsible for the initial perception of acute pain and the neuronal changes that rapidly lead to an increase in sensitivity of the injured region. At the same time, efforts to use combinations of analgesics and analgesic techniques including regional analgesia have been closely studied and shown to provide excellent pain relief. Despite our best efforts, some patients go on suffer from long-term chronic pain after the acute event. In this review, we will examine the basic physiologic mechanisms that lead to the perception of acute pain, our current understanding of the neuronal mechanisms that produce sensitization immediately after injury, and the risk factors that are associated with persistent pain after surgery. Our discussion will include an examination of the role for specific analgesic techniques in improving pain control in the immediate postoperative period and how we might identify those at greatest risk for persistent pain and develop analgesic regimens most likely to minimize the risk of persistent pain.

SENSITIZATION AND THE PROMISE OF PREEMPTIVE ANALGESIA

Pain is produced by physical, thermal, or chemical stimuli that can potentially induce tissue injury. Between the site of the stimulus and pain perception, a complex sequence of electrochemical events take place, which are collectively called nociception (Figure 1). Different stimuli can lead to the perception of pain. These include mechanical, thermal, and chemical stimuli. Mechanical forces, heat, and chemical changes result in increased firing in nerve terminals within tissue, this process is referred to as transduction.afferent axons carry signals from the site of peripheral stimulation toward the spinal cord where the signals are relayed to higher centers within the central nervous system. This process is called transmission. The magnitude of incoming nociceptive traffic reaching the central nervous system can be modified before reaching higher centers, a process termed modulation. Stimulation of the periaqueductal gray region within the midbrain and the periventricular gray matter lateral to the hypothalamus produces profound analgesia in humans. These regions have been found to contain high concentrations of endogenous opioid neurotransmitters. The periventricular gray matter and the periaqueductal gray matter are interconnected and also connect anatomically with the rostroventral medulla. The rostroventral medulla sends descending projections via the dorsolateral funiculus to the dorsal horn of the spinal cord. Norepinephrine, serotonin, and systemically administered opioids all likely produce their nociceptive effects through activation of these descending inhibitory pathways.

Preclinical studies have demonstrated that peripheral injuries can trigger long-lasting increases in the excitability of neurons, a process termed sensitization. This occurs both at the level of the primary afferent nociceptive peripheral neuron (peripheral sensitization) and the dorsal horn of the spinal cord (central sensitization). This is manifest as a reduction in the threshold for activation of nociceptive neurons; subsequently normally nonpainful stimuli are perceived as painful (allodynia) and minor painful stimuli now produce severe and long-lasting pain (hyperalgesia). This increase in gain in the nervous system, the sensitization, serves as a normal and protective response to injury. The sensitization is a reminder that the injured area needs to be protected to allow the tissue injury to proceed without interruption from repeated injury. In the absence of pain, like that seen in diabetics with loss of normal peripheral sensation who suffer from poorly healing ulcers in the extremities, recurrent injury goes unnoticed, healing is poor, and amputation of affected digits is common.

Under most circumstances, as injured tissue heals, sensitization gradually diminishes toward normal sensation. Nonetheless, persistent pain after injury is common. When pain persists along with the characteristics of sensitization after all tissue injury has healed, we call it neuropathic pain. The notion that the sudden barrage of incoming nociceptive traffic reaching the spinal cord is what leads to sensitization and that by applying an analgesic intervention before the traumatic event (surgical incision) we might reduce or even eliminate nociceptive traffic is what led to the concept of preemptive analgesia. We know when and where the surgical incision will take place. Can we reduce acute pain and maybe even prevent chronic pain from developing by giving an analgesic or performing a nerve block before the incision is made?

CLINICAL STUDIES OF PREEMPTIVE ANALGESIA

The term “preemptive preoperative analgesia” was coined in 1988 by Patrick Wall and the road to using this concept of preemptive analgesia to reduce the magnitude and duration of postoperative pain was paved in 1983 by Clifford Woolf, who showed evidence for a central component of postinjury pain hypersensitivity in experimental studies. It is now more than two decades since...
the concept of preemptive analgesia was put forward; the concept has been tested with different analgesics across many types of surgery. The basic approach is simple: randomize patients undergoing a specific type of surgery to receive the analgesic either before incision or at some time after the incision is made and measure their overall pain experience by following self-reported pain scores and/or supplemental analgesic use in the postoperative period. There are now more than 100 such trials of preemptive analgesia and numerous reviews. Two meta-analyses that appeared toward the end of the decade-long international focus on preemptive analgesia attempted to summarize the findings and both came away with less than exuberant enthusiasm for this approach. The first meta-analysis appeared in 2002; this group identified 80 randomized clinical trials of preincisional versus postincisional analgesic regimens for postoperative pain control conducted in 3,761 patients in total. The studies included 20 trials of systemic nonsteroidal antiinflammatory drugs (NSAIDs), 8 trials of systemic opioids, 8 trials of systemic N-methyl-d-aspartate receptor antagonists, 24 trials of epidural, caudal, or intrathecal analgesia, and 20 trials of peripheral local anesthetic use (wound infiltration or nerve block) or combinations of treatment. They rigorously defined successful preemptive analgesia as a weighted mean difference in the total sum of pain scores during the first 24 hours after surgery and they also examined total supplemental analgesic use during the same time period. They concluded that statistical improvements in postoperative pain relief were observed in some parameters or time points in 24 of 80 (82 treatment arms) trials when preemptive analgesia was compared with postoperative analgesia. However, no evidence for preemptive treatment with NSAIDs, IV opioids, IV ketamine, peripheral local anesthetics, and caudal analgesia to be of any benefit with respect to postoperative pain relief compared with a similar postincisional treatment. More than half of the trials of single-dose epidural treatment showed statistically significant but small and clinically unimportant improvements with preemptive analgesia.

A subsequent meta-analysis by Ong et al. appeared in 2005, examining much the same group of studies examined by Moniche et al. in their 2002 publication. Sixty-six studies with data from 3,261 patients were analyzed. Three primary outcome measures were analyzed by this group: pain intensity scores, supplemental analgesic consumption, and time to first analgesic consumption. In contrast to Moniche et al. who summed all pain scores during the first 24 postoperative hours, Ong et al. accepted reduction in a single pain scores at any point in time after surgery to represent significant preemptive analgesia. When the data from all three outcome measures were combined, they concluded that preemptive administration of epidural analgesia, local anesthetic wound infiltration, and NSAID administration all provided significant preemptive effects. Epidural analgesia resulted in consistent improvements in all three outcome variables, preemptive local anesthetic wound infiltration and NSAID administration improved analgesic consumption and time to first analgesic request, but not postoperative pain scores. Are these two major reviews at odds with one another? No, they simply defined a significant preemptive effect in differing ways: Moniche et al. used the more rigorous criteria of pain scores summed over the first 24 hours after surgery, perhaps a better measure of a truly meaningful clinical effect. While there may be statistically significant reductions in pain...
scores and supplemental analgesic use after surgery with use of a preemptive analgesic approach, these differences are small and are unlikely to impact on the patient’s overall pain experience. The largest differences appear early after emergence from anesthesia in the first few hours after surgery: if a preemptive approach was used, patients were more likely to emerge from anesthesia with good pain control. Perhaps the take-home message from this enormous body of work is simply that anesthesiologists should not wait until after emergence to begin, by whatever route is chosen, to administer analgesics.

Why doesn’t preemptive analgesia work? In a recent review, Katz et al.5 take us through the history of preemptive analgesia and posit a number of reasons that the overly simplistic approach of administering a single analgesic just before surgical incision is so inadequate in improving postoperative analgesia and other outcomes. They tell us that the classic view of preemptive analgesia assumes that intraoperative painful stimuli contribute to postoperative pain more than postoperative stimuli. But, experimental studies demonstrate that sensitization is caused by factors other than the incision and subsequent intraoperative events alone. Our focus should shift to reducing the impact of noxious preoperative, intraoperative, and postoperative events.

**PERSISTENT POSTSURGICAL PAIN: RISK FACTORS AND PREVENTION**

When pain persists for more than 3 to 6 months after surgery, normal postsurgical healing is complete, and there is no alternate ongoing process (e.g. infection) to explain the ongoing pain, persistent postsurgical pain (PPP) is present.6 PPP is surprisingly common after many of the most frequently performed surgeries (Table 1).

We know much about the preoperative risk factors that are predictive of the appearance of PPP. Risk factors include the magnitude and location of the surgical insult, genetic susceptibility, preceding pain, psychosocial factors, age and gender. Indeed, recent studies clearly demonstrate that patients with specific single nucleotide polymorphisms have a genetically conferred resistance to both acute and chronic pain.7 Despite advances in our understanding of what leads to persistent pain after surgery and the ease with which we can identify those at greatest risk, it is unclear how best to approach the management of pain during the perioperative period in a way that will minimize the risk of persistent pain.

**FROM PREEMPTIVE TO PREVENTATIVE ANALGESIA**

The limited approach provided by preemptive analgesia, simply providing the analgesic before the incision is made, may minimally improve pain relief, but is unlikely to reduce the incidence of persistent pain after surgery. The concept of preventative analgesia has emerged during the past few years. The idea is to combine a number of different analgesics with mechanisms that differ and that may well impact directly on the mechanisms behind development of persistent pain in efforts to improve postoperative pain control and prevent the development of persistent pain.4 A few trials suggesting that such a preventative approach may be effective have appeared. Lavand’homme et al.8 randomized patients undergoing colectomy to receive a combination of analgesics including local anesthetics, opioids, and clonidine IV or via neuraxial administration and examined the effect on postoperative hyperalgesia surrounding the surgical incision as well as persistent pain as far as 12 months after surgery. The use of epidural analgesia as part of a multimodal regimen dramatically reduced the incidence of persistent pain at 12 months after surgery, suggesting that this multipronged, preventative approach might well improve on the original concept of preemptive analgesia. Subsequent clinical trials using the same approach have yielded conflicting results. Buvanendran et al.7 demonstrated that the use of oral pregabalin during the immediate perioperative period in patients undergoing total joint replacement reduced the incidence of persistent pain several months after surgery, again emphasizing that specific analgesics continued through the perioperative period might well reduce the long-term problem of PPT. These small, preliminary studies show promise, but need confirmation through large-scale, multicenter trials.

**FUTURE DIRECTIONS**

Major trials are now underway that incorporate prospective identification of risk factors into analgesic trials. If we identify high-risk patients through genetic screening or by specific characteristics known to correlate with the development of persistent pain after surgery, will we be able to modify the outcome? As anesthesiologists in practice today, we can do nothing more than design the very best analgesic regimens with the tools we have at hand (regional anesthesia, systemic opioids and adjuvant analgesics) and trust that our efforts will succeed. When our initial approach proves inadequate, we should rapidly shift gears and provide

| Estimated incidence of chronic postoperative pain and disability after selected surgical procedures (adapted with permission from Reference 6). †National Center For Health Statistics, Ambulatory and Inpatients Procedures, USA, 1996. |
|---------------------------------|---------------------------------|---------------------------------|
| Amputation                      | Estimated incidence of chronic  |
|                                 | pain                          |
|                                 | Amputation                     |
|                                 | Estimated chronic              |
|                                 | pain                           |
|                                 | severe                         |
|                                 | (disabling) pain (>5 out of    |
|                                 | score of 10)                   |
|                                 | United States surgical volumes |
|                                 | (1000s)†                       |
| Thoracotomy                     | Estimated incidence of chronic  |
|                                 | pain                          |
|                                 | Thoracotomy                    |
|                                 | Estimated chronic              |
|                                 | pain                           |
|                                 | severe                         |
|                                 | (disabling) pain (>5 out of    |
|                                 | score of 10)                   |
|                                 | United States surgical volumes |
|                                 | (1000s)†                       |
| Coronary artery bypass surgery  | Estimated incidence of chronic  |
|                                 | pain                          |
|                                 | Intracranial repair            |
|                                 | Estimated chronic              |
|                                 | pain                           |
|                                 | severe                         |
|                                 | (disabling) pain (>5 out of    |
|                                 | score of 10)                   |
|                                 | United States surgical volumes |
|                                 | (1000s)†                       |
| Cesarean delivery               | Estimated incidence of chronic  |
|                                 | pain                          |
|                                 | Cesarean delivery              |
|                                 | Estimated chronic              |
|                                 | pain                           |
|                                 | severe                         |
|                                 | (disabling) pain (>5 out of    |
|                                 | score of 10)                   |
|                                 | United States surgical volumes |
|                                 | (1000s)†                       |
Is There a Link Between Acute Pain and Chronic Pain?

analgesia through some alternate means; removing and replacing a nonfunctioning epidural promptly or switching to IV opioids as quickly as possible to avoid periods of prolonged inadequate analgesia. In the very near term, we are likely to gain a better understanding of how to take those identified as at high risk for a poor pain experience and combine our existing analgesic approaches into a tailor-fit prescription for each patient that will minimize the chances of poor analgesia and persistent pain.

REFERENCES

Perioperative Management of the Morbidly Obese

Raviraj Raveendran, MBBS* and Frances Chung, MBBS FRCPC†

INTRODUCTION
Obesity is defined as a Body Mass Index (BMI) > 30 kg/m², morbid obesity is > 35 kg/m², super morbid obesity is >50 kg/m² and ultra-obesity is >70 kg/m². As per World Health Organization statistics, overweight and obesity are the fifth leading risk factor for global deaths with 1 in 10 of the world’s adult population being obese. Morbidly obese patients have significant comorbid conditions and cardiopulmonary changes that affect the pulmonary and cardiovascular system. Excess accumulation of fat in various locations in the body causes mechanical and metabolic problems. The mechanical problems such as alteration in pulmonary function, obstructive sleep apnea (OSA) and difficult airway challenge the anesthesiologist more than the metabolic problems such as hypertension, dyslipidemia and insulin resistance. Both these factors increase morbidity in the intraoperative and postoperative setting.

PHYSIOLOGICAL CHANGES
Obesity has a significant effect on the physiology of breathing. There is significant reduction in lung compliance as the result of increased pulmonary blood volume, closure of dependent airways and increased alveolar surface tension due to the reduction in functional residual capacity (FRC). But, the chest wall compliance is reduced in spontaneous breathing and normal in anesthetized, paralyzed subjects. Regarding lung volumes, there is a reduction in FRC due to the mass load of adipose tissue around the ribcage, abdomen and the visceral cavity. Residual volume is relatively well preserved with minimal reduction in total lung capacity. Tidal volumes are often reduced in severe obesity, and breathing follows a rapid, shallow pattern. As the FRC is low, closing capacity exceeds the FRC, and airway closure can occur within the tidal breaths. As BMI increases, there is a reduction in expiratory flow and a decrease in forced expiratory volume in 1 Second (FEV1) and forced vital capacity (FVC). But the ratio of FEV1 to FVC is preserved. Carbon monoxide-diffusing capacity is normal or increased due to increase in pulmonary blood flow. The airway resistance is also significantly higher in the obese and it is related to the reduction in lung volume rather than airway obstruction. There is an increase in ventilation-perfusion (V/Q) mismatch in the dependent lower lung zone, since it is under-ventilated and over-perfused. Subjects with simple obesity have an enhanced respiratory drive, while the respiratory drive of subjects with obesity hypoventilation syndrome (OHS) is either depressed or inappropriately suppressed.

CARDIOVASCULAR CHANGES
Obesity is independently associated with left ventricular hypertrophy, characterized by an increase in both left ventricular cavity size and wall thickness. An increase in left ventricular size also leads to atrial fibrillation. Anorexigenic drugs used to facilitate weight loss are associated with mitral and aortic valve regurgitation. In addition, myocardial contractility is reduced with diastolic dysfunction. Abdominal obesity is a well-defined risk factor for the development of atherosclerotic coronary artery disease. In obese patients, stroke volume and cardiac output are both increased, due to metabolic demand. Sympathetic activation likely results from sleep apnea and it prevents the normal nocturnal decline in arterial blood pressure. In general, obesity leads to hypertension, the probable mechanism is activation of the renin-angiotensin system which may occur directly via signals from adipose tissue.

Sleep apnea associated with obesity could lead to left ventricular hypertrophy, hypertension, increased sympathetic tone, chronic hypoxemia, and exaggerated swings in intrathoracic pressure during obstructive episodes. The increase in right ventricular cavity size and wall thickness is related to obstructive sleep apnea (OSA).

PREOPERATIVE ASSESSMENT
Morbidly obese patients are considered at high risk for perioperative complications and often undergo extensive testing for preoperative clearance, including chest radiograph, pulmonary function tests, noninvasive cardiac testing, and blood work. Although recent data indicate that extensive preoperative testing may not be necessary for every severely obese patient undergoing gastric bypass surgery, basic screening tests are imperative to identify the additional risk factors. Further preoperative testing should be individualized based on comorbid conditions. Since nearly 70% of morbidly obese patients are prone to have OSA. A screening test to diagnose and quantify OSA has been suggested to be mandatory. The “gold standard” for diagnosing OSA is overnight polysomnography. Since it is a time-consuming and expensive test, the STOP-Bang questionnaire (Table 1) can be used as a screening tool. The STOP-Bang questionnaire has the highest methodological validity and reasonable accuracy in predicting a diagnosis of OSA. A STOP-Bang score of 5–8 identified patients with high probability of moderate/severe OSA (Figure 1). The addition of serum HCO3-level ≥ 28 mmol/L to a STOP-Bang score ≥ 3 improves the specificity for preoperative OSA recognition. We propose a two-step screening process. The first step uses a STOP-Bang score to screen patients and the second step uses serum HCO3- in those with a STOP-Bang score ≥ 3 for increased specificity. Patients with a positive STOP-Bang questionnaire are more likely to have increased postoperative complications. The Oxygen Desaturation Index from a high resolution nocturnal oximeter is also a sensitive and specific tool to detect undiagnosed sleep-disordered breathing in surgical patients. Comorbidities associated with OSA are arterial hypertension, coronary artery disease, cerebrovascular disease, congestive heart failure, cardiac dysrhythmias and

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Perioperative Management of the Morbidly Obese

Diabetes mellitus.16 Studies suggest that patients with OSA, who have been treated with continuous positive airway pressure (CPAP) preoperatively, have fewer perioperative complications than those who are untreated.17 A functional algorithm could help to guide possible screening and the management of obese patients with OSA.18 Morbidly obese patients with OSA are prone to difficult intubation. But, a recent study of bariatric surgical patients has shown that there was no relationship between the severity of OSA, BMI, or neck circumference and difficulty of intubation. Only a Mallampati score of 3 or 4 and male gender predicted difficult intubation.19

OHS is defined by the triad of obesity, daytime hyperventilation and sleep-disordered breathing without an alternative neuromuscular, mechanical or metabolic cause of hypoventilation. It is a disease entity distinct from simple obesity and OSA. OHS is often undiagnosed but its prevalence is estimated to be 10–20% in obese patients with OSA and 0.15–0.3% in the general adult population. Compared to eucapnic obese patients, OHS patients present with severe upper airway obstruction, restrictive chest physiology, blunted central respiratory drive, pulmonary hypertension and increased mortality. The mainstay of therapy is noninvasive positive airway pressure.20

PREOPERATIVE PREPARATION

Preoperative sedative premedication should be avoided in morbidly obese patients with OSA. Obese patients have faster gastric emptying time, a large gastric volume and a frequent incidence of gastroesophageal reflux disease making them prone to aspiration. This risk increases further after bariatric surgery.21 If concerned about the risk of acid aspiration, H2-receptor antagonists or a proton pump inhibitor can be given. Also, obese patients are at significant risk of venous and pulmonary thromboembolism and therefore mechanical and pharmacological methods of perioperative thromboembolic prophylaxis must be considered.

The health care team should have special training in the issues relating to the care of morbidly obese patients. Patients should be encouraged to move themselves whenever possible. The operating table, trolley, bed and specific equipment such as a spine frame for spine surgery should be checked and labeled for its maximum weight-bearing capacity. An “obesity pack” (including specific equipment, protocol guidelines and contact numbers) should be available for emergency surgeries.

INTRAOPERATIVE MANAGEMENT

Airway management. Weight or BMI is just one of several factors to consider during an airway evaluation. A neck circumference larger than 43 cm is associated with an increased risk of difficult intubation.22 It is imperative to know the severity of OSA to predict the difficulty in mask ventilation and intubation. According to Brodsky et al,23 patients with a BMI > 35 kg/m² have a six-fold higher risk for difficult laryngoscopy. However, Mashour et al24 showed that there was no difference in difficult laryngoscopy in patients with BMI < 40 kg/m² versus > 40 kg/m².

Positioning with the head, neck and shoulders elevated in the head elevated laryngoscopy position (“HELP”) facilitates direct laryngoscopy. In morbidly obese patients,

| Table 1: Obstructive Sleep Apnea Screening Tools |
|--------------------------|--------------------------|
| **STOP-Bang Questionnaire** | **Yes** | **No** |
| S | Snoring: Do you snore loudly (louder than talking or loud enough to be heard through closed doors)? |
| T | Tired: Do you often feel tired, fatigued, or sleepy during daytime? |
| O | Observed: Has anyone observed you stop breathing during your sleep? |
| P | Blood Pressure: Do you have or are you being treated for high blood pressure? |
| B | BMI: Body Mass Index more than 35 kg/m²? |
| A | Age: Age over 50 years old? |
| N | Neck circumference: Neck circumference greater than 40 cm? |
| G | Gender: Male? |

At risk of OSA: Yes to 3 or more questions for STOP-Bang. Adapted from F Chung et al. Anesthesiology 2008;108:812–21
oxygen saturation after oxygen administration decreases more rapidly during apnea than in those with a normal BMI. This effect can be limited by a 25 degree head-up position during oxygen administration, the combination of oxygen administration with reverse Trendelenberg position and nasopharyngeal oxygen insufflation, positive end-expiratory pressure (PEEP) of 10 cm H2O and noninvasive bilevel positive airway pressure. Rapid sequence induction of anesthesia remains essential in morbidly obese patients with gastroesophageal reflux. In a series of 150 consecutive morbidly and super-obese patients, awake fiberoptic intubation was used in only 6–7% of patients at high risk of difficult intubation. Videolaryngoscopic-guided intubation with the Glidescope, Storz V-Mac or McGrath systems has a high success rate in morbidly obese patients with a difficult airway.

**PHARMACODYNAMIC AND PHARMACOKINETICS OF ANESTHETICS**

Physiologic changes in obesity affect distribution, protein binding and elimination of the various anesthetic drugs. Obese patients have a smaller than normal fraction of total body water, increased blood volume, cardiac output and larger than normal fat content. In addition, glomerular filtration rate is increased and hepatic clearance is usually normal or increased. In general, lipophilic drugs have a large volume of distribution based on the total body weight and hydrophilic drug (muscle relaxant) dosing is based on lean body weight. A recent study of rocuronium confirmed that the dose should be calculated based on ideal body weight. Similarly cisatracurium and vecuronium dosing are based on the ideal body weight. Since the levels of pseudocholinesterase and extracellular fluid space are increased in obesity, succinylcholine dose is calculated based on total body weight.

The volume of distribution of remifentanil in obese patients is less than expected, probably because of hydrolysis by blood and tissue esterases and dosing is based on the ideal body weight. A recent pharmacokinetic model of propofol in morbidly obese patients showed that total body weight was the major determinant of clearance. Benzodiazepines are highly lipophilic drugs. A single IV dose is based on total body weight, but if a continuous infusion is used, the dose should be adjusted based on the ideal body weight rather than total body weight because the total clearance is not substantially changed as compared with non-obese subjects. Sevoflurane and desflurane have lower lipid solubility than isoflurane and similar emergence and recovery profiles in morbidly obese patients.

**VENTILATION STRATEGIES**

After induction of anesthesia, atelectasis increases from 1 to 11% of total lung volume in morbidly obese patients. Recruitment maneuvers (PEEP and Valsalva) can counteract these effects. In one study the decrease in the compliance of the respiratory system and PaO2 was significantly reverted by the application of sustained inspiratory pressure combined with PEEP, but not by either intervention alone. During bariatric surgery, pressure-controlled ventilation improves oxygenation compared with volume control.

**POSITIONING**

The prone position is usually well tolerated by obese patients, since it helps to unload abdominal viscera and reduces pressure on the diaphragm, which improves FRC. The lateral position is also relatively well tolerated. Trendelenburg position decreases total compliance and FRC, which leads to increased atelectasis and hypoxemia. Obese patients who are breathing spontaneously do not
tolerate the Trendelenburg position. Their airways should be intubated and ventilation controlled or assisted. In supine position an increase in BMI proportionally decreases the FRC, pulmonary compliance and increases the (V/Q) mismatch. These effects are significantly reverted by reverse Trendelenburg position. The lithotomy position increases intrabdominal pressure and compression of the lungs, which can further reduce chest wall compliance.

**FLUID BALANCE**
Perioperative fluid administration in morbidly obese patients has double-edged implications. On one side, fluid restriction may result in acute tubular necrosis and organ dysfunction, while on the other, excessive fluid may lead to postoperative pulmonary complications. But the evidence is limited in this issue. In the presence of pneumoperitoneum, urine output is not a useful guide and in general central venous pressure and pulmonary capillary wedge pressure are not sensitive to fluid challenge. Stroke volume variation-guided optimization may have critical significance in limiting excessive fluid administration in morbidly obese patients undergoing bariatric surgery. A recent study compared high-volume (10 ml/kg/hr) fluid therapy versus low-volume (4 ml/kg/hr) therapy in laparoscopic bariatric surgery patients and it did not find any significant difference between these two groups in postoperative renal function. Both groups had intraoperative oliguria, which was unresponsive to fluid administration.

**LAPAROSCOPIC SURGERY**
Morbidly obese patients have markedly reduced supine FRC, with a further decrease in the Trendelenburg position and insufflation of the abdomen with CO2. Morbid obesity and pneumoperitoneum have significant effects on respiratory mechanics, whereas PaO2 was adversely affected only by increased body weight. Repositioning the patient from the supine position into the Trendelenburg position had no effect on PaO2 either before or after abdominal insufflation. In non-obese patients the difference in PaCO2/ETCO2 was high with large tidal volumes (800ml), but in morbidly obese patients this difference was high with small tidal volumes. The endotracheal tube moves further down in morbidly obese patients during laparoscopic surgery and this is aggravated by the Trendelenberg position.

**THORACIC SURGERY**
Since morbidly obese patients already have a restrictive spirometry pattern, one-lung ventilation could further affect the pulmonary function. Since predictive spirometric values are not indexed to weight, they may be inappropriate in obese patients. A large double-lumen tube should be chosen to minimize airflow resistance during one-lung ventilation and it is better to choose the tube size based on radiological imaging rather than gender or height. One-lung ventilation is technically possible in the lateral position, since abdominal content falls away from the body and unloads the dependent diaphragm. Large tidal volume ventilation, intermittent alveolar recruitment, CPAP to the collapsed lung and PEEP to the ventilated lung could help to avoid hypoxia during one-lung ventilation. In general, morbidly obese patients are prone to postoperative pulmonary complications which could be increased with thoracic surgery.

**REGIONAL ANESTHESIA**
Regional anesthesia offers distinct advantages: Minimal airway manipulation, avoidance of anesthetic drugs with cardiopulmonary depression, reduced postoperative nausea and vomiting and reduced perioperative opioid requirements. However, the rate of block failure may increase incrementally with a higher BMI. Using ultrasound-guided regional anesthesia for peripheral nerve blocks in the obese population has led to improved success rates. To improve postoperative spirometry, epidural analgesia should be considered in obese patients undergoing laparotomy. Because 50–68% of post-bariatric surgery patients are prone to have vitamin K deficiency due to malabsorption, documentation of normal coagulation function is necessary for neuraxial blocks. In previous studies, obese patients required less local anesthetic in their epidural and subarachnoid spaces in order to achieve the same level of block when compared with non-obese controls. In a study of the impact of morbid obesity on epidural complications in labor, there was a higher incidence of systolic and diastolic hypotension and prolonged fetal heart rate decelerations. However, a recent study showed no difference in spinal bupivacaine requirement between obese and non-obese parturient.

**AMBULATORY ANESTHESIA**
At one time, patients with a BMI > 30 kg/m2 or more were considered unsuitable for ambulatory anesthesia. Currently more importance is given to the comorbid conditions than BMI alone. The American Society of Anesthesiologists (ASA) practice guidelines provide risk assessment for patients with OSA receiving ambulatory anesthesia. Points are given based on the severity of the OSA, the degree of invasiveness of the planned operation, and whether or not the patient will need a general anesthetic and postoperative opioid analgesia. The ASA recommended that patients with a score above five should not be considered candidates for ambulatory surgery. It may not be safe for patients with severe OSA, requiring postoperative narcotics, to have ambulatory surgery. A recent review recommends that the majority of OSA patients may have surgery with few adverse events. The Society for Ambulatory Anesthesia also published a consensus statement on preoperative selection of patients with OSA scheduled for ambulatory surgery.

**POSTANESTHESIA CARE**
Whenever possible, patients should be tracheally extubated while awake in the sitting position and transferred to an appropriate postoperative environment. Morbidly obese patients are prone to postoperative hypoxemia due to atelectasis. Though intraoperative lung recruitment maneuvers are important to avoid hypoxemia, CPAP in the postanesthetic care unit helps to improve oxygenation. Patients with OSA should be instructed to bring their CPAP or noninvasive positive-pressure ventilation equipment to the hospital.
It has been shown that postoperative lung function of bariatric surgery patients is better with Boussignac CPAP application on tracheal extubation in the operating room rather than in the postanesthetic care unit. Compared with the Venturi mask, the Boussignac CPAP mask improves the postoperative PaO2/FIO2 ratio in morbidly obese patients.

**POSTOPERATIVE PAIN MANAGEMENT**

Pain control is important in obese patients, since it allows early mobilization and reduces the risk of deep vein thrombosis and pressure ulcers. The use of IV patient-controlled analgesia is often inevitable in particular, if regional anesthetic techniques are not possible or difficult. Opioid administration is associated with increased perioperative airway obstruction and desaturations even without OSA. Epidural analgesia improves the spirometry in obese patients undergoing midline laparotomy. Similarly in cardiac surgery, patients with a BMI > 30 kg/m2 had better analgesia and improved respiratory variables with the use of thoracic epidural analgesia than with conventional opioid-based analgesia. A multimodal pain management approach is particularly favored in obese patients, non-opioid analgesics should be considered wherever possible. Combinations of acetaminophen and nonsteroidal antiinflammatory drugs, are superior to single-drug therapy. However, the use of nonselective nonsteroidal antiinflammatory drugs in bariatric surgeries should possibly be avoided because of a higher risk for gastric perforation. Although the evidence is limited for the use of adjuvants such as ketamine, lidocaine, clonidine, dexmedetomidine and gabapentin in the obese population, they could be viable options to reduce perioperative opioid consumption. As per ASA guidelines, continuous neuraxial opioids during patient-controlled opioid analgesia are best avoided in obese patients with OSA.

**CONCLUSION**

The morbidly obese are a special group of patients who need extra care during the perioperative period. Understanding their anatomical, physiological, metabolic and pharmacological changes are imperative for the anesthesiologist to modulate the anesthetic technique for better outcomes. Advancement in anesthesia technology such as video laryngoscopes, ultrasound and ventilatory modes in anesthesia workstations has made a dramatic improvement in the perioperative care of obese patients. At the same time advancement in minimally invasive surgery challenges the anesthesiologist, since most of the surgeries are being done as ambulatory procedures. A protocol practice and guidelines to manage morbidly obese patients could optimize their perioperative management. Further studies are required in fluid administration, one-lung ventilation and postoperative pain management in morbidly obese patients.

**REFERENCES**

22. Gonzalez H, Minville V, Delanoue K, Mazeron M, Concina D, Fourcade O. The importance of increased neck circumference
to intubation difficulties in obese patients. Anesth Analg 2008;106:1132–6, table of contents


24. Dixson BJ, Dixson JR, Carden JR, Burn AJ, Schachter LM, Playfair JM, Laurie CP, O’Brien PE. Preoxygenation is more effective in the 25 degrees head-up position than in the supine position in severely obese patients: a randomized controlled study. Anesthesiology 2005;102:1110–5; discussion 5A


36. Carvalho B, Collins J, Drover DR, Atkinson Ralls L, Riley ET. ED(50) and ED(95) of intrathecal bupivacaine in morbidly obese patients undergoing cesarean delivery. Anesthesiology 2011;114:529–35

37. ASA practice guidelines for the perioperative management of patients with obstructive sleep apnea. Anesthesiology 2006;104:1081–93

INTRODUCTION
Although clinical genetics has been incorporated into many fields of medicine, its effect in surgical patients is somewhat less investigated. Having said this, anesthesiologists have long recognized that the response of apparently similar patients to drugs and surgery/interventions can be highly variable. Indeed, a drug given at the same relative concentration to an array of patients results in varying physiologic responses, creating a classic bell-shaped effect curve (or more precisely a Gaussian distribution) of response. Today it is widely recognized that variation in both pharmacokinetic and pharmacodynamic response to drugs can be explained, at least in part, by genetic differences among individuals. Therefore this review aims to update the reader on new concepts in genomic medicine and how they might be relevant to the perioperative patient and the field of anesthesiology.

GENERAL DEFINITIONS
DNA, RNA, protein, and metabolites
Genetic material that controls composition of each individual human being, from cell to entire organism, is contained in the form of double-stranded deoxyribonucleic acid (DNA) in the cell nucleus in the form of chromosome pairs (23 total pairs including sex-determining chromosomes). Genes are stretches of DNA that ultimately encode a specific protein; encoded protein segments are called exons and long stretches of DNA sequence that appear before or in between exons are called 5'-regulatory or 5'-untranslated regions, and introns, respectively. While DNA is compacted by being wound tightly around histones, this tight packing intermittently unwinds so that transcription factors can bind to 5'-regulatory regions of DNA to initiate/modulate transcription of specific genes into single-stranded ribonucleic acid (RNA). RNA is then processed (spliced, polyadenylated, degraded) and transcribed to amino acids (3 nucleotides encode an amino acid), and ultimately assembled into strings of amino acids, or proteins. After various cellular modifications of proteins, which provide their spectrum of activity, protein action ultimately produces small molecules, or metabolites in the cell. Metabolites form the milieu in which chemical and biologic reactions occur; such small molecules are a measure of activation/inhibition of final physiological pathways in cells.

“Omics”
After sequencing the entire human DNA of a few individuals in 2000, scientists turned to massively producing DNA sequences from individual patients with and without disease. Such massive screening of DNA is termed “genomics” and studies using these large-scale efforts, clinical genomics. The next large scale tool to be added to the genomics toolbox were large arrays consisting of thousands of single-stranded RNA molecules, or fragments of such RNA, from cells or animal/human tissues. By comparing before/after conditions, changes in RNA quantities could be examined. Large-scale protein analysis has been more difficult technically since it involves predominantly the use of mass spectrometry which is more labor intensive; this field is called proteomics. Following suit, identification of hundreds of small molecules and metabolites in cells, predominantly by old-fashioned biochemistry methodologies, is called metabolomics. Since DNA analysis is by far the easiest and least expensive of these methods, many studies using DNA sequencing surfaced first, with RNA microarrays running a close second historically. From these 2 methods, fingerprints of the genomics of tumors and diseases in patients have begun to be derived. Ironically, however, the most logical way to examine diseases would be to start with metabolomics, since this is the milieu that is most often
changed with disease or acute insults. By understanding alterations in proteins and metabolites, a true signature of biomarkers is obtained. RNA microarrays can then be used to determine the mechanism and/or pathway by which such diseases occurred (rather than being primarily a diagnostic tool itself), particularly given the unstable nature of RNA in general. DNA alterations can ultimately be used as an inexpensive screening tool once such variation is linked with protein/metabolite change.

DNA sequence variation
Variation in DNA sequences may lead to alterations in protein sequence and function, and therefore form the basis of variability in disease expression and therapeutic efficacy. DNA variation can consist of single nucleotide polymorphisms (SNPs) which are alterations of a single base, or it can result from shortened (deletions) or extended repeat sequences (insertions) within DNA itself. Genome-wide association studies (GWAS) are performed routinely now and consist of sequencing thousands of short DNA sequences (markers) found throughout the entire human genome. Since there are approximately 23,000–30,000 genes in the human genome and much more regulatory DNA, even thousands of DNA fragments represent only a small fraction of total DNA. Fortunately DNA crossovers, where 2 paired chromosomes exchange DNA inherited from mother and father, occur in fairly large fragments of DNA/chromosomes. This creates stretches of DNA that travel together, called haplotypes. Because of this fact, once the human genome was sequenced, the next step was creating a haplotype map (hap map) since SNPs within a haplotype block are often able to predict the presence or absence of other genetic variants. The field is now beginning to move beyond inferred DNA sequence changes using haplotypes, to directly re-sequencing all exon sequences known to exist to refine DNA sequence variation important in disease versus controls. Such studies are the cutting edge methods being used today and are called “exomics,” and even more extensive sequencing in numerous individuals is called “deep sequencing.”

Mitochondrial DNA
Thus far we have been discussing only genomic DNA. It is interesting to note that mitochondria, the powerhouse of cells, contain their own DNA. Mitochondrial DNA encodes only 13 genes, is circular, single-stranded, and is inherited from maternal mitochondrial DNA (as opposed to genomic double-stranded DNA inherited from both mother and father), although >1000 proteins are related to mitochondrial DNA. It is interesting to note that proteins required for development of intact mitochondria are a mixture of protein products from genomic DNA as well as the 13 genes in mitochondrial DNA. Because of the importance of mitochondria in producing free radicals with ischemia/reperfusion injury, it is increasingly apparent that variation in genomic and mitochondrial DNA is critical in determining how an individual patient may respond to injury. This is a burgeoning field and will be increasingly important in both understanding mechanisms of disease as well as using genetic variability as predictors to outcomes after surgery.

MicroRNA
Adding complexity to gene regulation is the recent discovery of microRNAs (miRNAs) and other longer non-coding RNAs. miRNAs are small 18–25 nucleotide long non-coding RNAs that modulate gene expression levels in a sequence-specific manner via the binding of mature miRNAs to complementary mRNAs. This binding negatively regulates expression of specific genes by either degrading the bound target mRNA or directly inhibiting translation. Specific miRNAs have been implicated in cell differentiation, cell apoptosis/death, ischemia/reperfusion responses, fat metabolism, and carcinogenesis in various species. Presence/absence of specific miRNAs in tumors has been hypothesized to potentially predict clinical outcome with tumor resection/treatment and ultimate clinical outcome, although one recent study in non-small cell lung cancer suggests no predictive ability. miRNAs also play a critical role in controlling cardiac stress responses that lead to transcriptional and translational alterations in gene expression. Over-expression of various miRNAs in cardiomyocytes in vitro induces cardiac hypertrophy and overexpression of miR-195, a known stress-inducible miRNA, resulting in abnormal cardiac remodeling and heart failure in transgenic mice. These findings suggest that miRNAs are important regulators of cardiac function and represent potential therapeutic targets for heart disease.

UPDATE ON CLINICAL GENOMIC STUDY METHODS
Candidate gene association studies
The historical standard for clinical genetics studies is the association study, where the incidence of DNA genetic variants (predominantly SNPs in a few candidate genes) is examined between groups of individuals with and without a disease. Such studies require careful matching for clinical covariants such as presence/absence of chronic disease, active medications, population stratification (race, country of origin), age, sex, clinical intervention details, etc. While such studies have been powerful, they are notoriously difficult to replicate, requiring large numbers of patients and crisp definitions of clinical outcomes (which are sometimes difficult to assure from medical records alone). In addition, even when SNPs from several genes are examined, and interactions considered, ultimately investigators “guess” which genes may be most important in a disease and use those as the starting point. As has been pointed out by many, this introduces bias in that only “known” genes/pathways are considered rather than all possible mechanisms. As a result, targeted candidate association studies alone are increasingly difficult to publish unless replication in a separate group of individuals and/or associated biologic changes can be reported in the same study.

GWAS studies
GWAS, described initially above also examine groups of patients and control healthy individuals. But rather than examining targeted SNPs from a selected group of genes, GWAS specifically takes an unbiased approach by using thousands of GWAS markers spread across the entire genome. The theoretical advantage of such an approach is that novel pathways/factors can be elucidated that may be
important in either predicting disease or providing mechanistic insights. As with targeted association studies, large populations of patients must be studied, both cases and controls. This has been difficult since GWAS panels containing thousands of genes per patient are quite expensive. Also, even though thousands of SNPs are examined, this still means that potentially only 1 per 10,000 DNA nucleotides is studied. Since not all genetic variations are present in haplotypes with a study marker, or related to the marker SNP by linkage disequilibrium, important genetic variability can be missed. Hence this approach should be considered a first “low hanging fruit” approach where a positive may be meaningful for common genetic variants, but a negative result may not be helpful. Indeed, some have argued that large GWAS studies in hypertension, even those with >30,000 individuals studied, have neither illuminated key genes with significant biologic effects nor unlocked the genetic basis of the disease. One conclusion from these studies is that rare genetic variants may play a bigger role in “common” disease than was originally thought.

Whole exon sequencing

In order to study both common and rare SNPs in an unbiased way, recent studies have begun to resequence all known exons across the genome. While whole genome sequencing is rapidly decreasing in price, these studies remain extremely expensive. As a result, what is often done is to identify populations of patients with a range of quantitative phenotypes (clinical expression of disease) and examine the top and bottom 10% for comparison. For example, if arterial blood pressure is to be studied, perhaps 30 patients with the highest blood pressures and 30 with the lowest blood pressure might be examined. A major advantage of resequencing exons is that all forms of genetic variation in a given gene can be elucidated. Interestingly, genes encoding proteins known to be important in a given disease may have multiple ways they can become dysfunctional. Therefore a wide range of rare SNPs may represent various ways to mediate dysfunction of the same gene product (protein), but would technically be considered rare SNPs rather than common SNPs due to the percent occurrence individually.

Because of this phenomenon, whole exon sequencing may help the entire field of clinical genetics redefine common and rare variants over the next few years.

Importance of genetic controls for any clinical study

One important consideration that has come out of recent genetics trials is the concept of genetic controls. For example, if a trial is designed to examine the efficacy of a drug in a specific clinical setting, then it is important to ensure that genetic variability in drug-metabolizing enzymes is controlled within the trial. Otherwise efficacy of a drug might be mistakenly enhanced in patients who are less able to metabolize the active drug, and hence its concentration stays higher and longer. The opposite is true for drug side effects; they would be more common in patients unable to rapidly and effectively metabolize a given drug.

DIAGNOSING PRESENCE OF DISEASE-CAUSING AGENTS

One area where medicine and anesthesiology have benefited dramatically from genomic medicine advances is in diagnosis of pathogens causing disease. This is especially true in the intensive care unit where the presence of bacteria and viruses can be identified rapidly, including identification of specific strains. This is possible using diagnostic amplification of small fragments of DNA from these invading organisms. While normal flora must be considered, drug-resistant and highly virulent strains of bacteria can be identified now fairly rapidly, enabling treatment to be definitively initiated within hours of specimen testing. Diagnostic cultures often take several days, and can still be used for confirmation, but in many cases a more definitive antimicrobial agent can be started immediately. This decreases drug resistance within hospitals (by decreasing the use of broad-spectrum antibacterial agents) and helps to track strains present within outbreaks.

In the outpatient setting, diagnosis of sexually transmitted diseases has also been greatly enhanced using molecular genetic approaches to diagnose the presence and virulence of specific strains. Recent discoveries suggest a new mechanism of sexually transmitted disease may be infection by non-viral Trichomonas vaginalis which may itself be infected with up to 4 distinct strains of viral DNA, complicating overall disease expression. This type of information is crucial for modern day public health tracking and interventions.

Chronic disease patients also benefit from examination of pathologic infectious agents. For example, patients with cystic fibrosis often have gram negative lung infections since they have difficulty clearing their thick mucous secretions. A recent study examined the role of specific strains of Pseudomonas Aeruginosa in patients with cystic fibrosis and demonstrated that a common strain (Liverpool epidemic strain) is associated in England, Australia, and Canada with worse lung function, death and/or need for lung transplantation in this vulnerable population of patients. This information then provides the opportunity to intervene in such patients more rigorously.

CURRENT CLINICAL HUMAN DISEASE APPLICATIONS

Tumor diagnosis and treatment

Traditionally, tumor diagnosis has been accomplished using histology and pathologic methods. Such approaches have increasingly relied on antibodies capable of identifying tumor markers, which generally are proteins uniquely expressed in tumor cells and not in host tissue cells. However, since the genomic revolution, it has been recognized that genetic abnormalities in cells that ultimately go on to become cancerous can be harnessed for diagnosis and prediction of treatment options and efficacy. This has been true for childhood cancers for almost 2 decades since isolation of tumor cells in blood is rather easily available. However, it is a harder prospect for solid tumors. Hence new molecular findings relating molecular markers (predominantly DNA deletions and mutations) for specific brain tumors (gliomas) are encouraging since they appear to facilitate diagnosis, management, and predict outcome in low-grade gliomas.
In addition, in other studies involving neuroblastoma, the important prognostic role of the ABC11 (ATP-binding cassette subfamily C member1) gene for patient outcome has recently been suggested.12 Another example is breast cancer where BRCA gene mutations are well known to increase the risk of breast cancer in a subpopulation of patients, yet the majority of breast cancers without BRCA mutations remain difficult to categorize and, in those cases, treat.13 Molecular genetics of tumors is an important growth area in medicine and may be able to finally unlock adult solid tumors to the point of having better response to therapeutic intervention and ultimately better outcomes.

Cardiovascular disease
Many aspects of cardiovascular disease have a genetic component, ranging from coronary disease14 to familial peripheral arterial calcification,15 blood coagulation,16-18 and cardiovascular drug action. Even chronic coagulation, known to be important in the acquisition and progression of cardiovascular disease, has been examined in terms of “inflammasome-mediated disease.”19 In this review we highlight one example of a commonly used clinical genetics approach to two types of anticoagulation.

One of the more thoroughly investigated areas where genomic approaches have real impact on clinical practice is in the area of coagulation, specifically prediction of a starting dose for highly toxic drugs such as warfarin (coumadin)16 and use/efficacy of antiplatelet drugs such as clopidogrel.17,18 In these settings, genetic testing can reveal opposite situations. For warfarin, genotypes for warfarin metabolism and vitamin K (e.g. genotype variants of Cytochrome P450 metabolizing enzymes CYP2C9 and CYP4F2, as well as the vitamin K activating enzyme VKORC1 which requires less warfarin for inhibition) have been shown to be important in improving prediction of therapeutic warfarin dose and overall anticoagulation management versus standard clinical approaches.16 Because the improved prediction has great potential to limit warfarin’s side effects such as excessive bleeding and emergency room visits, genetic testing is becoming more routine as warfarin is initiated. For clopidogrel, an antiplatelet drug, it is usually therapeutic efficacy, rather than side effects, that is tested. Interestingly, clopidogrel is a pro-drug, so individuals with specific genetic variants cannot metabolize the pro-drug to active drug and hence do not respond with the expected antiplatelet activity. This results in lack of protection from myocardial infarction in the setting of unstable angina or interventions such as coronary artery stent placement. This risk is considered so high, and clopidogrel so common in this important clinical setting, that the Food and Drug Administration recently put a “black box” warning so that clinicians would be aware to prescribe alternative antiplatelet drugs to the subset of patients who are nonresponders. Only recently has genetic variability of the enzymes regulating metabolism of the active drug been also investigated as another source of variable clinical outcomes.

Translation of genomic findings from “bench to bedside”
It is difficult for the average clinician to keep up to date with new genetic information, specifically what genetic variants should be considered in drug therapies used to treat common diseases. With this in mind, almost 10 years ago the National Institutes of Health recognized the need to have researchers create and collate data on genetic variants important for drug action. They created a group of researchers called the Pharmacogenomics Research Network (PGRN), located at multiple sites across the United States, who participate in clinical genetics trials in various common, complex human diseases. Their findings are located on the PGRN website at the National Institutes of Health (http://www.nigms.nih.gov/Research/FeaturedPrograms/PGRN/) where clinicians can find the latest information on various different drug-metabolizing enzymes and other genetic variants important in drug action. Particularly helpful is the pharmacogenetics knowledge base (PharmGKB; http://www.pharmgkb.org/) which is frequently updated based on new results from PGRN investigators’ clinical trial findings. Data are annotated so clinicians can understand the strength of results and recommendations. Although this site is not meant to be used as the sole criteria for dosing a patient clinically, it does provide education, references, and definitive guidelines by the manufacturers, as well as results of interactions between various genetic variant combinations that might be present in a given patient. A specific subgroup of the PGRN is called the Clinical Pharmacogenetics Implementation Consortium, which is currently a group of 6 medical centers that are in the process of implementing at least one (and often several) common genetic variants into their electronic ordering system in order to give every clinician at their institution expert advice at the point of drug ordering.

Genetic variants reveal new mechanisms of disease
Naturally occurring human genetic variants can also provide insights into disease mechanisms. An example of this can be seen in α1-adrenergic receptors (α1ARs), which are G protein-coupled transmembrane receptors that mediate actions of the sympathetic nervous system through binding of endogenous catecholamines epinephrine and
norepinephrine. Among the 3 α₁AR subtypes, α₁ARs predominate in human vascular smooth muscle, particularly in resistant vessels.²⁴,²⁵ Vasoconstriction and vascular remodeling are precipitating factors in human hypertension, a major cardiovascular risk factor for developing heart disease and stroke. Stress-induced development of hypertrophy is characterized by changes in the structure of both blood vessels and heart. Recently it has been found that a genetic variant present in the 3rd intracellular loop of the human α₁aAR constitutively couples to a distinct biochemical pathway with enhanced cellular growth effects.²⁶ Such findings suggest that by discovering new pathways activated by genetic variants in physiological pathways, entirely new drug classes may be considered in the treatment of common diseases such as hypertension.

**CONCLUSION**

Clinical genetics has become part of mainstream medicine in many settings relevant to anesthesiologists. This brief review has highlighted key areas of medicine where genetic testing is routinely used for diagnosis, prediction of treatment efficacy, or elucidating more fundamental mechanisms of disease.

**REFERENCES**

Don’t Make Things Worse with Your Ventilator Settings: How You Manage the Lungs During the Perioperative Period Affects Postoperative Outcomes

Peter Slinger, MD, FRCPC

INTRODUCTION

Patients are at risk for several types of lung injury in the perioperative period. These injuries include atelectasis, pneumonia, pneumothorax, broncho-pleural fistula, acute lung injury and acute respiratory distress syndrome (ALI/ARDS). Anesthetic management can cause, exacerbate or ameliorate most of these injuries. Lung-protective ventilation strategies using more physiologic tidal volumes and appropriate levels of positive end-expiratory pressure (PEEP) can decrease the extent of this injury. In this review I will discuss the effects of mechanical ventilation and its role in ventilator-induced lung injury (VILI) with specific reference to patients with severe chronic obstructive pulmonary disease (COPD) requiring general anesthesia and surgery.

Chronic Obstructive Pulmonary Disease

The most common chronic respiratory illness in the surgical population is COPD which incorporates three disorders: emphysema, peripheral airways disease and chronic bronchitis. Any individual patient may have one or all of these conditions, but the dominant clinical feature is impairment of expiratory airflow. Assessment of the severity of COPD is on the basis of the FEV1% of predicted values. The American Thoracic Society categorizes Stage I >50% predicted stage II: 35–50%, and stage III <35 stage I patients should not have significant dyspnea, hypoxemia or hypercarbia and other causes should be considered if these are present.

Respiratory Drive

Many stage II or III COPD patients have an increased PaCO2 at rest. It is not possible to differentiate these “CO2-retainers” from nonretainers on the basis of history, physical examination or spirometric pulmonary function testing. This CO2-retention seems to be more related to an inability to maintain the increased work of respiration (Wresp) required to keep the PaCO2 normal in patients with mechanically inefficient pulmonary function and not primarily due to an alteration of respiratory control mechanisms. It was previously thought that chronically hypoxemic/hypercapnic patients relied on a hypoxic stimulus for ventilatory drive and became insensitive to PaCO2. This explained the clinical observation that COPD patients in incipient respiratory failure could be put into a hypercapnic coma by the administration of a high concentration of oxygen (FiO2). Actually, only a minor fraction of the increase in PaCO2 in such patients is due to a diminished respiratory drive, as minute ventilation is basically unchanged. The PaCO2 increases because a high FiO2 causes a relative decrease in alveolar ventilation and an increase in alveolar dead space and shunt by the redistribution of perfusion away from lung areas of relatively normal ventilation/perfusion (V/Q) matching to areas of very low V/Q ratio because regional hypoxic pulmonary vasoconstriction is decreased and also due to the Haldane effect. However, supplemental oxygen must be administered to these patients postoperatively to prevent the hypoxemia associated with the unavoidable decrease in functional residual capacity (FRC). The attendant increase in PaCO2 should be anticipated and monitored. To identify these patients preoperatively, all stage II or III COPD patients need an arterial blood gas analysis.

Nocturnal Hypoxemia

COPD patients desaturate more frequently and severely than normal patients during sleep. This is due to the rapid, shallow breathing pattern that occurs in all patients during rapid eye movement sleep. In COPD patients breathing air, this causes a significant increase in the respiratory dead space/tidal volume (Vd/VT) ratio and a decrease in alveolar oxygen tension (PAO2) and PaO2. This is not the sleep apnea hypoventilation syndrome (SAHS). There is no increased incidence of SAHS in COPD.

Right Ventricular (RV) dysfunction

RV dysfunction occurs in up to 50% of COPD patients. The dysfunctional RV is poorly tolerant of sudden increases in...
afterload such as the change from spontaneous to controlled ventilation. RV function becomes critical in maintaining cardiac output as the pulmonary artery pressure increases. The RV ejection fraction does not increase with exercise in COPD patients as it does in normal patients. Chronic recurrent hypoxemia is the cause of the RV dysfunction and the subsequent progression to cor pulmonale. Patients who have episodic hypoxemia in spite of normal lungs (e.g., central alveolar hypoventilation, SAHS, etc.) develop the same secondary cardiac problems as COPD patients. The only therapy which has been shown to improve long-term survival and decrease right heart strain in COPD is oxygen. COPD patients who have resting PaO2 <55 mmHg should receive supplemental home oxygen and also those general COPD patients who have resting PaO2 <55 mmHg should receive supplemental home oxygen and also those who desaturate to <44 mmHg with exercise. The goal of supplemental oxygen is to maintain a PaO2 60–65 mmHg. Compared to patients with chronic bronchitis, emphysematous COPD patients tend to have a decreased cardiac output and mixed venous oxygen tension while maintaining lower pulmonary artery pressures.

**Bullae**

Many patients with moderate or severe COPD develop cystic air spaces in the lung parenchyma known as bullae. These bullae will often be asymptomatic unless they occupy more than 50% of the hemithorax, in which case the patient will present with findings of restrictive respiratory disease in addition to their obstructive disease. A bulla is a localized area of loss of structural support tissue in the lung with elastic recoil of surrounding parenchyma. The pressure in a bulla is actually the mean pressure in the surrounding alveoli averaged over the respiratory cycle. This means that during normal spontaneous ventilation the intra-bulla pressure is actually slightly negative in comparison to the surrounding parenchyma. However, whenever positive-pressure ventilation is used the pressure in a bulla will become positive in relation to the adjacent lung tissue and the bulla will expand with the attendant risk of rupture, tension pneumothorax and bronchopleural fistula. Positive-pressure ventilation can be used safely in patients with bullae provided the airway pressures are kept low and there is adequate expertise and equipment immediately available to insert a chest drain and obtain lung isolation if necessary.

**Flow limitation**

Severe COPD patients are often “flow-limited” even during tidal volume expiration at rest. Flow limitation is present in normal patients only during a forced expiratory maneuver. Flow limitation occurs when an equal pressure point (EPP) develops in the intrathoracic airways during expiration. During quiet expiration in the normal patient the pressure in the lumen of the airways always exceeds the intrapleural pressure because of the upstream elastic recoil pressure which is transmitted from the alveoli. The effect of this elastic recoil pressure diminishes as air flows downstream in the airway. With a forced expiration the intrapleural pressure may equal the intraluminal pressure at a certain point, the EPP, which then limits the expiratory flow. Then, any increase in expiratory effort will not produce an increase in flow at that given lung volume.

Flow limitation occurs particularly in emphysematous patients, who primarily have a problem with loss of lung elastic recoil and have marked dyspnea on exertion. Flow limitation causes dyspnea because of stimulation of mechano-receptors in the muscles of respiration, thoracic cage and in the airway distal to the EPP. Any increase in the work of respiration will lead to increased dyspnea. This variable mechanical compression of airways by over-inflated alveoli is the primary cause of the airflow obstruction in emphysema.

Severely flow-limited patients are at risk for hemodynamic collapse with the application of positive pressure ventilation due to dynamic hyperinflation of the lungs. Even the modest positive airway pressures associated with manual ventilation with a bag/mask at induction can lead to hypotension since these patients have no increased resistance to inspiration but a marked obstruction of expiration. In some of these patients this has contributed to the “Lazarus” syndrome in which patients have recovered from a cardiac arrest only after resuscitation and positive-pressure ventilation was discontinued.

**Auto-PEEP**

Patients with severe COPD often breathe in a pattern that interrupts expiration before the alveolar pressure has decreased to atmospheric pressure. This incomplete expiration is due to a combination of factors which include flow-limitation, increased work of respiration and increased airway resistance. This interruption leads to an increase of the end-expiratory lung volume above the FRC. This PEEP in the alveoli at rest has been termed auto-PEEP or intrinsic-PEEP. During spontaneous respiration the intrapleural pressure will have to be decreased to a level which counteracts auto-PEEP before inspiratory flow can begin. Thus, COPD patients can have an increased inspiratory load added to their already increased expiratory load.

Auto-PEEP becomes even more important during mechanical ventilation. It is directly proportional to tidal volume and inversely proportional to expiratory time. The presence of auto-PEEP is not detected by the manometer of standard anesthesia ventilators. It can be measured by end-expiratory flow interruption, a feature available on the newer generation of intensive care ventilators. Auto-PEEP has been found to develop in most COPD patients during one-lung anesthesia. Paradoxically it has been found that a small amount of added PEEP (e.g. 5cmH2O) can decrease Auto-PEEP and hyperinflation in many ventilated COPD patients.

**Preoperative therapy of COPD**

There are four treatable complications of COPD that must be actively sought and therapy begun at the time of the preanesthetic assessment. These are: atelectasis, bronchospasm, respiratory tract infections and pulmonary edema. Atelectasis impairs local lung lymphocyte and macrophage function predisposing to infection. Pulmonary edema can be very difficult to diagnose by auscultation in the presence of COPD and may present very abnormal radiological distributions (unilateral, upper lobes, etc.). Bronchial hyper-reactivity may be a symptom of congestive failure or may be an exacerbation of reversible airways
obstruction. All COPD patients should receive maximal bronchodilator therapy as guided by their symptoms. Only 20–25% of COPD patients will respond to corticosteroids. In a patient who is poorly controlled on sympathomimetic and anticholinergic bronchodilators, a trial of corticosteroids may be beneficial.

Physiotherapy: Patients with COPD have fewer postoperative pulmonary complications when a perioperative program of intensive chest physiotherapy is initiated preoperatively. Among the different modalities available (cough and deep breathing, incentive spirometry, PEEP, continuous positive airway pressure [CPAP] etc.) there is no clearly proven superior method. Family members or nonphysiotherapy hospital staff can easily be trained to perform effective preoperative chest physiotherapy and this should be arranged at the time of the initial preoperative assessment. Even in the most severe COPD patient, it is possible to improve exercise tolerance with a physiotherapy program. Little improvement is seen before one month. Among COPD patients, those with excessive sputum benefit the most from chest physiotherapy.

A comprehensive program of pulmonary rehabilitation involving physiotherapy, exercise, nutrition and education can improve functional capacity for patients with severe COPD. These programs are usually several months duration and are generally not an option in resections for malignancy although for nonmalignant resections in severe COPD patients, rehabilitation should be considered. The benefits of short duration rehabilitation programs before malignancy resection have not been fully assessed. Smoking: Pulmonary complications are decreased in thoracic surgical patients who cease smoking for >4 weeks before surgery. Carboxyhemoglobin concentrations decrease if smoking is stopped >12 hr. It is extremely important for patients to avoid smoking postoperatively. Smoking leads to a prolonged period of tissue hypoxemia. Wound tissue oxygen tension correlates with wound healing and resistance to infection. There is no rebound increase in pulmonary complications if patients stop for shorter (<8 week) periods before surgery.

Postoperative Analgesia: It was initially theorized that thoracic epidural analgesia (TEA) could diminish the diaphragmatic inhibition, which is known to occur after thoracotomy. Such disinhibition was shown for TEA after upper abdominal surgery. Indeed a postthoracotomy animal study demonstrated similar disinhibition. However, a postthoracotomy study of patients with moderate COPD failed to show any improvement of diaphragmatic contractility by TEA even though respiratory function (tidal volume) was improved. This is not easy to explain but it may be similar to the concept of increasing cardiac output without increasing myocardial contractility by changing loading conditions for the ventricle. The diaphragm inserts on the chest wall, and by decreasing chest splinting the diaphragm may be returned to a mechanically more efficient position on its force-length (Starling) contraction curve without affecting its actual contractility.

In patients with severe emphysema it has been shown that analgesic doses of TEA bupivacaine do not cause any significant reduction in lung mechanics or increase in airway resistance. In volunteers a thoracic level of epidural blockade increased FRC. This increase is largely due to an increase in thoracic gas volume caused by a decrease in the resting level of the diaphragm without a decrease in tidal volume. This contradicts earlier studies, which found no change in FRC with TEA. The different results are probably related to the more advanced methodology of the more recent work. FRC is considered the most important determinant of oxygenation in the postoperative period. Although it is possible to deliver an opioid to the spinal cord receptors via a lumbar catheter in adequate amounts for analgesia, the beneficial effects of local anesthetics on respiratory mechanics require a thoracic catheter.

The only large randomized prospective study of epidural versus systemic analgesia was the MASTER trial performed in Australia, mainly for upper abdominal surgery. Postoperative respiratory failure was significantly reduced in the epidural group (23% vs. 30%) with no differences in other types of complications or mortality. This beneficial effect of thoracic epidural analgesia seems to be most pronounced in patients with underlying lung disease such as COPD. In a retrospective propensity-based analysis of patients with COPD who had major abdominal surgery, the use of TEA was associated with a lower incidence of postoperative pneumonia (11% vs. 16%) and a lower 30-day mortality (5% vs. 9%). This trend also seems to apply to thoracic surgery where a retrospective analysis found TEA was associated with a three-fold decrease in respiratory complications in COPD patients after lung resection. A large retrospective review of more than 80,000 surgical patients in the Ontario Health Insurance database found a small significant reduction in overall mortality related to the use of epidural anesthesia and analgesia (1.7% vs. 2%) and this difference was most notable in thoracic and orthopedic surgery.

**Mechanical Ventilation**

Historically, anesthesiologists have been taught to ventilate patients’ lungs in the perioperative period with relatively large tidal volumes. Volumes as high as 15ml.kg⁻¹ ideal body weight have been suggested to avoid intraoperative atelectasis. This far exceeds the normal spontaneous tidal volumes (6ml.kg⁻¹) common to most mammals. Several studies have identified the use of large tidal volumes as a major risk factor for development of lung injury in mechanically ventilated patients without ALI. Gajic et al. reported that 25% of patients with normal lungs ventilated in an intensive care unit setting for 2 days or longer developed ALI or ARDS. The main risk factors for ALI were use of large tidal volumes, restrictive lung disease and blood product transfusion. A prospective study from the same group has found that tidal volumes >700mls and peak airway pressures >30cm H2O were independently associated with the development of ARDS. An intraoperative study of patients having esophageal surgery compared the use of tidal volumes of 9 ml.kg⁻¹ without PEEP during two- and one-lung ventilation (OLV) versus 9 ml.kg⁻¹ during two-lung ventilation and 5 ml.kg⁻¹ during OLV with PEEP 5 cmH2O throughout. They found significantly lower serum makers of inflammation (cytokines interleukin (IL)-1β, IL-6 and IL-8) in the lower tidal volume plus PEEP group. The study did not find any major difference in postoperative
outcome between the two groups; however it was not powered to do this. The study did demonstrate better oxygenation in the lower tidal volume group during and immediately after OLV, but not after 18h. In a study looking at conventional versus protective ventilation in critically ill patients without lung injury, de Olivera et al. randomized patients to ventilation with either 10-12mL.kg⁻¹ or 6-8mL.kg⁻¹ predicted body weight. In both groups a PEEP of 5 was applied and the FiO₂ titrated to keep SpO₂ > 90%. At 12 hours after ventilation, inflammatory markers in broncho-alveolar lavage fluid (tumor necrosis factor α and IL-8) were significantly higher in the larger tidal volume group. Choi et al. compared 12mL.kg⁻¹ without PEEP versus 6mL.kg⁻¹ with 10cm PEEP and showed procoagulant changes in lavage fluid of the larger tidal volume group after 5 hours of mechanical ventilation. A randomized-control trial in 150 critically ill patients without ALI compared tidal volumes of 10mL.kg⁻¹ versus 6mL.kg⁻¹ predicted body weight. The conventional tidal volumes were associated with a sustained plasma increase in inflammatory cytokines.

Of importance is work suggesting that noninjurious or so-called “protective ventilatory settings” can induce lung injury in previously healthy lungs. An animal study using a very elegant murine “one hit” VILI model, showed that even the least injurious lung settings induced biochemical and histological changes consistent with lung injury. Work with rodents undergoing mechanical ventilation showed significant gene expression (including genes involved in immunity and inflammation) after only 90 minutes of protective ventilation. Whether this has an impact on clinical outcome is unknown at this time.

ALI is the most common cause of postoperative respiratory failure and is associated with markedly decreased postoperative survival. A prospective case controlled study by Fernandez-Perez et al. looking at intraoperative ventilator settings and ALI after elective surgery in more than 4000 patients found a 3% incidence of ALI in high-risk elective surgeries. Compared with controls, patients with ALI had significantly lower postoperative survival rates and increased length of hospital stay. Interestingly in this study, intraoperative peak airway pressure, but not tidal volume, PEEP or FiO₂ were associated with ALI. A retrospective cohort study looking specifically at intraoperative risk factors for ARDS in critically ill patients found that for patients receiving fluid resuscitation > 20mL.kg⁻¹.hr⁻¹ the odds of developing ARDS were 3 times greater than if < 10mL.kg⁻¹.hr⁻¹ was given (odds ratio 3.1, 95% CI = 1.0-9.9 p = 0.05). Tidal Volume.Ideal Body Weight (Vt.IBW⁻¹) (ml.kg⁻¹) and number of blood products were not associated with ARDS in this study. Of interest the majority of patients’ lungs were ventilated with a Vt.IBW⁻¹ of 8-10mL.kg⁻¹ and an intraoperative PEEP of 0.

**Ventilator Induced Lung Injury**

The phenomenon of VILI is well recognized, and can be particularly significant in surgical specialties that require large transfusions, cardiopulmonary bypass and associated lung ischemia-reperfusion injury (IRI). The deleterious effects of mechanical ventilation may be mediated by localized inflammation and the systemic release of inflammatory cytokines (bio-trauma). Mechanical stretch from cyclic alveolar opening and closing sets up an inflammatory response in the alveolar epithelial cells and the vascular endothelial cells. Hyperinflation causes nuclear translocation of Nuclear Factor-κB (a key regulator of the expression of multiple genes involved in inflammatory response) and up-regulation of other proinflammatory cytokines. Polymorphonuclear leukocyte recruitment and activation appear to be key component of the mechanical stretch induced inflammatory response. The balance between apoptosis and necrosis is unfavourably altered by both ischemia-reperfusion and mechanical stretch.

Bio-trauma not only aggravates ongoing lung injury but also has important systemic consequences due to the spill over of these inflammatory mediators into the systemic circulation, inducing remote organ dysfunction. A study evaluating novel mechanisms of remote organ injury resulting from VILI showed that mechanical ventilation can lead to epithelial cell apoptosis in the kidney and the small intestine with accompanying biochemical evidence of organ dysfunction. In mice undergoing injurious mechanical ventilation, alveolar stretch induced adhesion molecules not only in the lung but also in the liver and kidney. In addition, cytokine and chemokine expression in pulmonary, hepatic and renal tissue after mechanical ventilation was accompanied by enhanced recruitment of granulocytes to these organs. These studies go some way to explain the remote organ dysfunction seen with ALI/ARDS, and the role optimizing ventilatory strategies play in ameliorating this.

This leads to the question; are the lung-protective strategies in ARDS applicable to the perioperative environment, specifically in patients with healthy lungs? A study analyzing this question highlights the lack of randomized controlled trials looking at best intraoperative tidal volume, PEEP, and use of intraoperative lung recruitment. While outcome studies are lacking, based on what we know about the effects of mechanical ventilation, it seems not unreasonable to aim towards protective ventilatory strategies in perioperative practice.

**Perioperative surgical environment factors**

There are multiple factors in the surgical environment that can contribute to lung injury. The most obvious being the surgical approach. Site of operation is an important predictor of pulmonary complications, with upper abdominal and thoracic incisions being the most important (any surgery approaching the diaphragm). A decrease in respiratory complications has been documented if major cavity procedures can be done with minimally invasive versus open techniques. Atelectasis occurs frequently after open surgical procedures and in up to 90% of patients undergoing general anesthesia. It is a pathological state that can contribute to or attenuate lung injury. Thus anesthesiologists must be aware of techniques to avoid or treat it. While open to debate, retrospective and prospective studies have shown that appropriate thoracic epidural analgesia reduces the incidence of respiratory complications (atelectasis, pneumonia and respiratory failure) after major abdominal and thoracic surgery. The benefits of epidural analgesia seem to be in direct proportion to the severity of
the patients’ underlying lung disease. Patients with COPD seem to derive the most benefit from epidural analgesia. Reviews comparing paravertebral block versus epidural analgesia in patients undergoing thoracic surgery showed equivalent analgesia efficacy but a better side effect profile and lower complication rate with paravertebral block.\textsuperscript{59,60} Aggressive physiotherapy with CPAP in the postoperative period in patients after major abdominal surgery who develop early desaturation leads to decreased rates of major respiratory complications.\textsuperscript{61}

**Role of Volatile Anesthetic Drugs in Lung Protection**

Volatile anesthetics have immune-modulatory effects. Much work has been done, especially in the cardiac setting, on the role of volatiles in IRI and in pre- and postconditioning. Studies in models of ALI, during OLV and in cases of lung ischemia-reperfusion suggest that volatile anesthetics may act as pre- and postconditioning drugs inducing lung protection by inhibition of the expression of proinflammatory mediators. Isoflurane pretreatment in an endotoxin-mediated animal model of lung injury exerted protective effects, as evidenced by reduction of polymorphonuclear recruitment and microvascular protein leakage.\textsuperscript{63} Postconditioning with sevoflurane attenuated lung damage and preserved lung function in an in vivo rat ALI model.\textsuperscript{64} In a prospective study, patients undergoing thoracic surgery with OLV were randomized to either propofol or sevoflurane anesthesia.\textsuperscript{65} Observing inflammatory markers in the nonventilated lung, they found an attenuated inflammatory reaction. Significantly, the sevoflurane group had improved outcome and significantly lower overall number of adverse events. A study comparing OLV (Vt 10ml.kg\textsuperscript{-1}) with desflurane versus propofol anesthesia observed the inflammatory response in the ventilated lung.\textsuperscript{66} The inflammatory markers IL-8, IL-10, PMN elastase and TNF\alpha were significantly lower in the desflurane group.

While much work remains to be done, this exciting work does point towards a role for volatile anesthetics in attenuating the proinflammatory response in the lungs to a host of insults, whether this is pre, during or postinsult.

**Ultra-protective Lung ventilation**

Following along the continuum of lung-protective ventilation in ALI/ARDS is the concept of ultra-protective ventilation. This concept uses pumpless extracorporeal lung assist, specifically the Novalung\textsuperscript{®} ILA membrane ventilator, and near static ventilation. A brief description of the Novalung\textsuperscript{®} is appropriate; it is a membrane ventilator that allows O\textsubscript{2} and CO\textsubscript{2} gas exchange via simple diffusion.\textsuperscript{67} The membranes are biocompatible and provide a non-thrombogenic surface. It is designed to work without a mechanical pump in an arteriovenous configuration, thus requiring an adequate mean arterial blood pressure to drive flow. Flow rates are typically 1-2L.min\textsuperscript{-1}, or approximately 15% of cardiac output. CO\textsubscript{2} clearance is controlled by varying the oxygen flow rate. It must be noted that oxygenation may be variable and may not be sufficient in severe hypoxic disorders. As compared with conventional extracorporeal membrane oxygenation, the Novalung\textsuperscript{®} is a simple, pumpless portable device. Anticoagulation requirements are much reduced with an activated partial thromboplastin time target of 55s. Bleeding complications and blood product requirements are significantly less.

ARDNent and animal data demonstrate that lower tidal volumes (3ml.kg\textsuperscript{-1}) compared with 6-12ml.kg\textsuperscript{-1} significantly reduce endothelial and epithelial injury.\textsuperscript{68,69} In other words “protective” tidal volumes can still induce VILI. However clearance of CO\textsubscript{2} and oxygenation become an issue at these lower minute volumes. The Novalung\textsuperscript{®} allows for this marked reduction in minute volumes and the simultaneous correction of PaCO\textsubscript{2} and pH. An animal model of post-pneumonectomy ARDS using the Novalung\textsuperscript{®} and tidal volumes of 2.2mls.kg\textsuperscript{-1} and respiratory rate of 6 showed significantly better outcomes compared with conventional lung-protective strategies.\textsuperscript{70} Case reports in humans in a variety of clinical scenarios have been encouraging.\textsuperscript{71} Tidal volumes \(\leq 3\)ml.kg\textsuperscript{-1}, low inspiratory plateau pressure, high PEEP and low respiratory rates are all possible with the Novalung\textsuperscript{®} in situ, causing less VILI and subsequent remote secondary organ failure. The use of extracorporeal membrane oxygenation in combination with protective ventilation has been shown in a randomized trial to significantly increase the survival rate to 63% versus 47% with conventional ventilation strategies, in patients with severe ARDS.\textsuperscript{72}

**Fluids, Inflammation and the Glycocalyx**

A retrospective cohort study looking specifically at intraoperative risk factors for ARDS in critically ill patients found that for patients receiving fluid resuscitation > 20ml.kg\textsuperscript{-1}.hr\textsuperscript{-1} the odds of developing ARDS were 3 times greater than if < 10ml.kg\textsuperscript{-1}.hr\textsuperscript{-1} was given (odds ratio 3.1, 95% CI = 1.0–9.9 p = 0.05).\textsuperscript{73} Vt.IBW\textsuperscript{-1} (ml.kg\textsuperscript{-1}) and number of blood products were not associated with ARDS in this study. Of interest the majority of patients’ lungs were ventilated with a Vt.IBW\textsuperscript{-1} of 8-10ml.kg\textsuperscript{-1} and an intraoperative PEEP of 0. It has long been a concern that excess amounts of IV fluids predispose patients to develop ALI.

However, it has been a conflicting concern for anesthesiologists that fluid restriction in thoracic surgery may contribute to postoperative renal dysfunction which was reported to be associated with a very high (19%) mortality.\textsuperscript{74} In a review of >100 pneumonectomies at our institution, acute kidney injury (AKI) as defined by the RIFLE classification\textsuperscript{75} occurred in 22% of patients.\textsuperscript{76} However, there was no association of AKI with fluid balance and there was no increased 30-day mortality in the AKI patients. AKI was associated with preoperative hypertension and complex surgical procedures such as extrapleural pneumonectomy. A similar retrospective study looking at all pulmonary resection patients found that AKI, as defined by the Acute Kidney Injury Network criteria, which occurred in 67/1129 (6%) patients was not associated with a statistically significant increase in mortality versus non-AKI patients (3% vs. 1%).\textsuperscript{77}

Fluid requirements vary widely among patients and procedures and ultimately represent the sum of preoperative deficits, maintenance requirements, and ongoing losses. Fluid management for major esophageal surgery is particularly challenging. Preoperative fluid deficits in patients with severe esophageal disease may be substantial, though they have not been well defined.\textsuperscript{78} Fluid requirements in patients
undergoing esophageal procedures may be complicated by the fact that patients may be relatively hypovolemic after long preoperative fasts, particularly if esophageal obstruction or dysphagia limit fluid intake. Perioperative losses occur via a number of mechanisms including urinary, gastrointestinal, evaporative losses, bleeding, and interstitial fluid shifting. This shift of fluid from the vascular compartment into the interstitial space accompanies surgical trauma and is likely to reflect vascular injury and loss of endothelial integrity. So called “third space” losses describe fluid loss into noninterstitial extracellular spaces which are not in equilibrium with the vascular compartment and thus considered to be a “nonfunctional” extracellular fluid compartment. However, it is very possible that the third space does not exist and was described as a result of measurement errors in early studies of the fluid compartments in the body.79

One of the factors complicating fluid management for esophageal resection is that thoracic epidural analgesia has been shown to improve outcome for these patients80 but its use tends to contribute to hypotension. Hypotension is well known to contribute to ischemia of the gut anastomosis81 and treatment with excessive fluids is likely to exacerbate the problem.82 Many surgeons are concerned about the effects of vasopressors on the anastomotic gut blood flow.83 However, several animal studies suggest that treatment of intraoperative hypotension with norepinephrine does not cause any reduction of gut blood flow in the presence of normovolemia.84,85

An ideal fluid regimen for major surgeries, including esophageal surgery, is individualized and optimizes cardiac output and oxygen delivery while avoiding excessive fluid administration. There is some evidence that fluid therapies which are designed to achieve individualized and specific flow-related hemodynamic endpoints such as stroke volume, cardiac output, or measures of fluid responsiveness such as stroke volume variation (collectively referred to as goal-directed fluid therapy) may provide a superior alternative to fixed regimens or those based on static measures of cardiac filling, such as central venous pressure which does not predict fluid responsiveness or correlate with circulating blood volume after transthoracic esophagectomy.86,87

In addition to the potential importance of the amount and timing of fluid administration, there is some clinical evidence that the choice of fluid type may be important in affecting clinical outcomes.88 Intravascular colloid retention during treatment of hypovolemia may approach 90% versus 40% when administered during normovolemia.90

The relationship of hydrostatic and oncotic pressure to determine fluid flux across a semi-permeable membrane was described in a classic equation developed in 1896 by Starling.89 Several clinical observations such as the relative resistance of the intact organism to develop edema and the inability of therapy with hyperoncotic agents to draw fluid from the pulmonary interstitium into the vascular compartment are not explained by the Starling formula.90 This discrepancy is now attributed to the glycocalyx, a micro-cilial layer that lines the endothelium and acts as a molecular sieve. This layer tends to increase the oncotic pressure on the inner surface of the endothelium and decrease leukocyte and platelet adhesion to the endothelium. The glycocalyx deteriorates during IRI and in the presence of a wide variety of inflammatory mediators such as cytokines and probably contributes to the increased vascular permeability seen in these situations. Also, the glycocalyx deteriorates in the presence of atrial natriuretic peptide and may explain the increase in plasma protein filtration that has been seen with colloid boluses. Protecting the glycocalyx may be among the anesthesiologist’s most important duties perioperatively. Volatile anesthetics may have a protective effect on the glycocalyx.91

Other therapies for lung protection
Beyond those already discussed, there are several therapies that may play a future role in lung protection. Permissive hypercapnia’s place in protective ventilation has been alluded to earlier, but as found in the original ARDSnet data, may be protective in the presence of higher tidal volumes.52 Hypercapnic acidosis is protective in a variety of models of ALI. Beneficial effects include attenuation of lung neutrophil recruitment, pulmonary and systemic cytokine concentrations, cell apoptosis and free radical injury.93 Inhaled hydrogen sulfide shows beneficial effects in a model of VILI via the inhibition of inflammatory and apoptotic responses, independent of its effects on body temperature.94 Inhaled aerosolized activated protein C in a sheep model of ALI demonstrated improved oxygenation as well as lung aeration (as assessed by computed tomography scan).95 ß-adrenergic agonists have potential benefits by increasing the rate of alveolar fluid clearance by increasing cellular cyclic adenosine monophosphate and have antiinflammatory properties.96 A randomized controlled trial in 40 patients with ALI showed a decrease in extravascular lung water and plateau airway pressure with IV salbutamol, although it showed no differences in outcome.97 A randomized placebo-controlled trial of several different therapies including surfactant, prone positioning, inhaled nitric oxide and antiinflammatories has not shown significant clinical benefits in patients with established ALI.98 While it is unreasonable to expect there to be a single therapy (or “magic bullet”) that will prevent ALI, the above exciting research does hold promise in both furthering our understanding and management of injured or at risk lungs.

Summary
To summarize what we know:

1. Nonphysiological ventilation in healthy lungs induces ALI.
3. Protective lung ventilation in noninjured lungs and in the absence of a primary pulmonary insult may initiate VILI (as evidenced by inflammatory markers)
4. VILI has important implications remote to the lungs and may be associated with significant morbidity and mortality.
5. Volatile anesthetics may have a lung-protective effect
6. Excess fluids may contribute to perioperative lung injury.
Anesthesiologists manage a heterogeneous group of patients in the perioperative period; from patients with healthy lungs, and patients with “at risk” lungs, through to patients with severe COPD. More patients are at risk for ALI during surgery than previously thought. Appropriate perioperative management may prevent or ameliorate this lung injury. Applying protective ventilatory strategies seems reasonable based on our current understanding of mechanical ventilation and lung injury.

REFERENCES

34. TENNEY SM, REMMERS JE. Comparative quantitative morphology of the mammalian lung: diffusing area. Nature 1963;197:54–6


89. Starling EH. On the Absorption of Fluids from the Connective Tissue Spaces. J Physiol 1896;19:312–26
Anesthesia for Common Pediatric Surgical Emergencies: Are You Well Equipped?

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The operating room (OR) is an environment where all cases are performed. Perhaps the most difficult ones are the pediatric emergencies. Most children and infants differ from adults in several aspects. (i) they do not, at most times, have a history of anesthetic exposure; (ii) they are generally healthy and do not have cardiopulmonary problems. This leads to a scenario where they are healthy yet have underlying pathology that leads to a potential for rapid deterioration in their conditions. This paper will deal with 4 major clinical pediatric emergency scenarios that are seen in most hospitals that may lead to rapid alteration in a child’s condition. (Table 1)

Preoperative preparation: It is important to understand a few common themes with all of these patients. This includes any family history of complications associated with anesthesia including, but not limited to, a history of malignant hyperthermia. In addition, a thorough history of experiences with anesthesia as well as any associated abnormalities including congenital heart disease and other congenital anomalies is important to obtain before providing anesthesia. Preoperative fasting guidelines are important, however, except for pyloromyotomy, most of these patients will have some degree of urgency and will require rapid anesthetic care. It is important to also keep in mind that the presence of trauma can decrease gastric emptying time. The main caveat in urgent versus emergent surgery is to recognize the nature of intervention needed and the condition of the patient.

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 first-born 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.1

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 fontanelle. In addition, due to significant vomiting, it is important to ensure that the child is also not hypoglycemic at the time of presentation. It is important to hydrate the child before induction of anesthesia. The surgery is urgent but never emergent.

Induction and maintenance of anesthesia: A rapid sequence induction is generally planned. It is important to ensure that the stomach is adequately suctioned before induction of anesthesia. Oxygen administration is important 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. The debate of whether to use succinylcholine versus a nondepolarizing drug like rocuronium has been studied.2 The time to recovery may be slightly prolonged with the nondepolarizing drug. It is also important to assess the surgical technique for the procedure. In the event it is a laparoscopic procedure, careful attention has to be paid to the insufflation pressures for the abdomen. Higher pressures may lead to compression of the inferior vena cava leading to a further decrease in arterial blood pressures. A subumbilical approach has been compared to a laparoscopic technique, the laparoscopic technique may lead to a faster recovery and a shorter operating time.3 Total IV anesthetic (TIVA) versus inhaled anesthetics have been studied in this population demonstrating a rapid return to baseline with ultra-short-acting opioids like remifentanil.4 We have used transversus abdominal plane blocks for managing pain in the postoperative period thereby avoiding opioids for the surgery.

Emergence and postoperative care: Emergence from surgery and a fully awake patient. Maintaining an IV access is important for the infant to ensure absence of hypoglycemia in the immediate postoperative period. These children do very well and often have a rapid recovery to their normal state within hours of surgery.

Airway foreign body: Airway foreign body is perhaps the most common emergent procedure in children besides trauma. Most presentations of airway foreign bodies occur later than the actual ingestion of the foreign body. There is usually a history of cough or persistent wheezing, or an occasional history of ingestion. Very rarely there is stridor or significant desaturation.5 It is important to recognize “when, what and where” the aspiration happened.6 The common rule of thumb is (i) the foreign body is often organic; (ii) lodged in the bronchial tree; (iii) right side having a higher propensity than the left side; few are radio-opaque (11%); and they have a mortality of about 0.42%.6

Preoperative evaluation: A plain film of the chest may be obtained by the emergency department doctor before consultation of the ear-nose-throat service.7 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 difficult 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
Table 1: Common pediatric emergencies

<table>
<thead>
<tr>
<th>Procedure</th>
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<tbody>
<tr>
<td>Airway foreign body</td>
</tr>
<tr>
<td>Pyloric stenosis</td>
</tr>
<tr>
<td>Supracondylar fracture for closed reduction</td>
</tr>
<tr>
<td>Tonsillectomy with bleeding</td>
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</tbody>
</table>

Three techniques include inhaled induction with spontaneous ventilation; TIVA using propofol and remifentanil; and using manual jet ventilation. If possible, IV access is usually obtained in the emergency. A smooth mask induction with spontaneous ventilation with sevoflurane and nitrous/oxygen is then performed. After securing the airway, it is crucial to allow for spontaneous ventilation since there is a potential for dislodging the foreign body during retrieval. Factors leading to hypoxemia include younger patient, plant seed as foreign body, long surgical duration, pneumonia during the procedure and in some instances spontaneous ventilation. Ventilatory modes, especially jet ventilation, may potentially benefit children. TIVA has been associated with breath holding, longer duration of emergence and potential for laryngospasm. Maintenance can be achieved using inhaled anesthetics or IV infusions.

Foreign Body Removal: The foreign body can be removed using several techniques. The common technique is to use a rigid ventilating bronchoscope with a forceps to retrieve the foreign body. 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 use 1% lidocaine spray for the cords before airway instrumentation.

Postoperative complications: These include laryngeal edema, bronchospsasm, hypoxic cardiac arrest, pneumothrax, pneumo-mediastinum, tracheal and bronchial laceration. It is imperative that there is communication with the surgeon before and during the procedure. The outcome of the child is based on proper communication as well as the superb skills of the surgeon and the anesthesiologist.

Bleeding Tonsils: This is an unfortunate event after a routine tonsillectomy in children. There are many factors that may lead to bleeding including poor hemostasis, bleeding diathesis including von Willebrand disease that is not diagnosed, infection, and foreign body irritation. Tonsillar bleeding occurs in 2 phases, an early phase that is associated with poor hemostasis or bleeding issues, and a secondary bleed that occurs in the first week, which is associated with secondary infection. Sixty-six percent of bleeding occurs in the tonsillar bed, 27% in the nasopharynx and 7% where it is combined. The incidence was about 2.15% in a large retrospective analysis. In addition, there is a Cochrane analysis that has demonstrated that there is a bleeding association with the use of nonsteroidal antiinflammatory drugs.

Preoperative preparation: Although this seems like an emergency, it is imperative to stabilize the patient before induction of anesthesia. Patients are often dehydrated and may have a low hemoglobin count. It is imperative that the fluid status is first assessed. In addition, it is important to remember that the child is anxious and nervous. Intravenous catheter placement is important before the induction of anesthesia. As mentioned earlier, it is important to make sure that the patient is well hydrated. 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 crossmatch 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.

Induction of anesthesia: The child is likely to be anxious. It is important to hydrate the patient before induction of anesthesia. 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. An IV rapid sequence induction is usually planned with either propofol or ketamine (if the child is unstable) and succinylcholine or high dose rocuronium. A stylet is used for the endotracheal tube. 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 bleeding profile as well as an international normalized ratio. This may reveal a potential for a bleeding diathesis. We prefer giving some antiemetic before tracheal extubation since these patients have a propensity to vomit after surgery.

Postoperative period: This is one of those instances where a routine outpatient procedure can change to an inpatient admission. It is important to observe these patients for at least 6 hours after surgery.

Supracondylar fracture reduction: This is a common presentation to an emergency department in the Summer months. Most of these children are healthy and have sustained an injury while in a playground or at school. They present with significant pain and may require immediate surgery.

Preoperative preparation: NPO time is important. The presence of a traumatic event can lead to a decrease in gastric emptying thereby leading to a potential full-stomach patient. In addition, it is important for the surgeon to determine if there is a need for checking the vascular supply or the potential for nerve damage. There are simple tests for checking the integrity of the radial nerve (thumbs up sign), ulnar nerve (crossing the fingers); and median nerve (completing a circle with the index finger and thumb).

Anesthesia induction: Since most of these patients are not emergent but urgent, they are generally scheduled during working hours except if there is any significant loss or absent pulses or if there is a propensity for compartment syndrome. A laryngeal mask airway is generally acceptable. After reduction of the fracture, we place an indwelling IV catheter in the supraclavicular area using saline to highlight the area of needle placement. Once the child is awake and alert, we do the neurocheck before injection of local anesthetic solution.
Conclusions: Pediatric emergencies are generally more difficult than adult situations due to the need to calm the child as well as provide an optimal scenario for providing care. As more noninvasive techniques are being designed, surgery may become more relevant in certain cases than others.

**REFERENCES**

Controversies in Pediatric Anesthesia

Santhanam Suresh, MD, FAAP

Upper respiratory tract infections (URI) are common in toddlers and infants and are the main reason for visits to the emergency room or pediatricians’ offices. This is a large population that presents for routine surgery in the pediatric population. In recent years, with the advent of more potent influenza viral seasons we have seen many children affected with viral infections especially during the winter months. There is an association with the presence of reactive airway disease in children who are recovering from a recent cold or URI.

Preoperative evaluation: Preoperative evaluation should consist of listening to the child’s lungs for rhonchi or wheezing. The potential for a lower respiratory tract infection after a URI is relatively common in children. It is also important to determine if there is a history of asthma or wheezing. Children who are exposed to common colds are at greater risk for reactive airway disease and can hence have a greater propensity for wheezing or bronchospasm during anesthesia. (Table 1)

Many attempts have been made to prevent side effects during the presence of a URI. This includes the use of bronchodilators and antisialagogue such as glycopyrolate or atropine. In one study, the group that received glycopyrolate had the advantage of earlier discharge from the postanesthesia care unit (PACU) as opposed to the group that did not receive the drug. There were no significant differences in adverse events in children in the study group as opposed to the placebo group (45.2% vs 37.5%). The data are sparse and current randomized trials have demonstrated no differences in outcomes after pretreatment with any of the measures.

Induction of anesthesia: A mask induction is preferred because this allows for a smooth induction. Using induction drugs such as ketamine can lead to more secretions and potential airway obstruction. As mentioned earlier, the use of glycopyrolate or atropine has not demonstrated better outcomes. Many of these children may be presenting for minor procedures such as myringotomy with a pressure equalizer tube placement who may not require the need for IV access. It is imperative that the anesthesiologist is prepared for the potential of rapid intervention in the event the patient develops laryngospasm.

Airway intervention: URI is frequent in children who are presenting for adeno-tonsillectomy. The potential for laryngospasm and desaturation after extubation has prompted research into alternatives other than endotracheal tubes for the procedure. The flexible laryngeal mask airway has been successfully used in our institution for adeno-tonsillectomy as an airway device. There was no added benefit for the use of supraglottic devices compared to an endotracheal tube in a large retrospective study when contrasted to a previous study that demonstrated superiority of the laryngeal mask airway over an endotracheal tube. There has been ongoing debate as to whether extubating a patient with a URI under deep anesthesia may be more beneficial to extubating while wide awake. In an interesting randomized controlled trial, the investigators found no difference in the incidence of complications in either group. There was an increased incidence of coughing in children who were extubated awake versus those extubated under deep anesthesia (60% in wake vs. 35% in deep anesthesia extubation). However, the incidence of airway obstruction in deeply anesthetized patients was more frequent than awake extubation (26% vs. 8%).

Postoperative Management: It is important to recognize that children with URIs may be prone to desaturation in the postoperative period. In addition, they may be prone to bronchospasm, stridor or persistent coughing. It is important to keep this in mind while dealing with these children in the PACU because they may require additional postoperative observation.

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Table 1. Risk Factors in a Child with an Upper Respiratory Tract Infection

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
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<tbody>
<tr>
<td>History of asthma</td>
<td></td>
</tr>
<tr>
<td>Recent croup</td>
<td></td>
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<tr>
<td>High fever (bacterial infection)</td>
<td></td>
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<tr>
<td>Airway surgery or airway maneuvers</td>
<td></td>
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<tr>
<td>History of obstructive sleep apnea</td>
<td></td>
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<tr>
<td>Major prolonged surgery</td>
<td></td>
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<tr>
<td>Eczema</td>
<td></td>
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<tr>
<td>Passive smoking</td>
<td></td>
</tr>
</tbody>
</table>

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REFERENCES

Tighten Your Belts! Reduce Your Transfusion Costs with Preoperative Management of Anemic Patients

Thomas R. Vetter, MD, MPH

CURRENT BEST PRACTICES IN PERIOPERATIVE PATIENT-CENTRED BLOOD MANAGEMENT

Blood management has been defined by the Society for Advancement of Blood Management as “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.” Formalized blood management is being driven by, and gaining momentum because of, known and unknown blood risks; preservation of a local, regional and national blood supplies; and escalating blood product costs.2,3

Approximately 15 million packed red blood cell (PRBC) units are transfused annually in the United States and 85 million are transfused annually worldwide.4,6 However, blood transfusion practices vary widely and often do not follow current evidence-based best practices.7 Furthermore, while blood transfusion is a mainstay of treating surgical blood loss, it is not without risk, especially in developing countries with inadequate screening of donor blood.7,8 An increasing number of patients thus refuse blood products, seek autologous donation, or request so-called “bloodless surgery” due to the perceived risk of blood transfusion.8

Known risks of allogeneic transfusions include transmissible infectious agents, transfusion reactions, and effects on immunomodulation (e.g., postoperative infection and tumor progression).3 Not surprisingly, the risks associated with allogeneic PRBC transfusions differ significantly among countries with a low versus high human development index (HDI): an index based on life expectancy, literacy, enrollment in further education, and per capita income.8 In countries with a low HDI, the risk of infection (human immunodeficiency virus, hepatitis B, hepatitis C, and malaria) is increased, whereas in countries with a high HDI, immunological reactions (hemolytic transfusion reactions, alloimmunization and immunosuppression) are predominant.8

Published data also support a major association between intraoperative blood transfusion and morbidity and mortality in patients undergoing noncardiac surgery.10 A recent retrospective analysis examined the association between blood transfusion and 30-day morbidity and 30-day mortality, in patients undergoing general, vascular, or orthopedic surgery. Compared with patients who were not transfused, patients receiving one or two units of erythrocytes were significantly more likely to have pulmonary complications (adjusted odds ratio, aOR of 1.76), sepsis (aOR of 1.43), thromboembolic complications (aOR of 1.77), and wound complications (aOR of 1.87).10

Intraoperative blood transfusion was also associated with a significantly increased risk of death (aOR of 1.29), with a similar increased risk of 30-day composite morbidity (aOR of 1.23 and NNH of 3) and 30-day mortality (aOR of 1.32 and NNH of 11) were observed in the 2005–2006 American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) database of general surgery patients.31 While these data are disconcerting, such association does not equate to causation. Nevertheless, efforts to reduce or to eliminate the need for surgical blood transfusion are very critical.12

The most important predictor of blood transfusion in surgery is the preoperative circulating erythrocyte mass, as estimated by the patient’s hemoglobin (Hgb).3 Thus not surprisingly, preoperative anemia is also an independent predictor of postoperative morbidity and mortality.3,13–15 Based upon the 2008 ACS NSQIP database, preoperative anemia was independently associated with an increased risk of 30-day morbidity (aOR of 1.35) and 30-day mortality (aOR of 1.42) in patients undergoing major noncardiac surgery.15

Of note, this significantly increased risk of morbidity and mortality was present with mild anemia (hematocrit > 29% and < 39% in men and > 29% and < 36% in women) and moderate-to-severe anemia (hematocrit ≤ 29% in men and women).15 An even stronger association between anemia (Hgb < 13.0 g/dL for men and < 12.0 g/dL for women) and increased 90-day mortality (aOR of 2.36) was observed in a retrospective Canadian health system cohort of noncardiac surgery patients.13

Preoperative anemia is a common condition among surgical patients; however, its reported prevalence varies widely, ranging from 5% to 75% depending on the type of surgery, the patient’s age, gender, co-morbidities, as well as the criteria used for defining anemia.16,17 The most frequent causes for existing preoperative anemia are iron deficiency and anemia of chronic disease.18,19 In a national audit of patients undergoing elective orthopedic surgery in the United States, 35% were found to have Hgb of < 13 g/dL at the time of preadmission testing.20–22 A recent systematic review observed an average 24% prevalence of preoperative anemia in total joint replacement patients, resulting in a 45% perioperative transfusion rate.23

Lastly, with the ageing of the population in the United States, and other developed countries, voluntary blood donation pools and rates continue to decrease,24 which will likely increase the occurrence of acute blood shortages and elective surgery cancellations.18,25,26 This shrinking donor availability, combined with measures to reduce the risks of infection transmission (e.g., increasingly restrictive donor screening criteria) have increased the direct costs of blood products.26,27 It has been estimated that the total cost per unit of PRBC is in excess of $1000 ($250 acquisition cost X 4), resulting in annual hospital expenditures of $1.63 to $6.03 million.28

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Given these various motivating factors, patient blood management (PBM) (i.e., “blood conservation”) is thus being widely advocated.26,29,30 PBM has been defined by Society for Advancement of Blood Management as “the appropriate provision and use of blood, its components and derivatives, and strategies to reduce or avoid the need for a blood transfusion.”1 This concerted effort is better termed, patient-centered blood management,31 to reflect the increasing emphasis on patient-centeredness in other areas of medicine and the consumer-perspective of health care.32–34

PBM incorporates an evidence-based approach that is multidisciplinary (anesthesiology, critical care medicine, surgery, and transfusion medicine) and multiprofessional (physicians, nurses, pump technologists, and pharmacists).3,29,32–36 PBM focuses on the treatment of the individual patient and comprises goal-directed transfusion therapy and appropriate pharmacotherapy.18,37 PBM is fundamentally based on three strategies or pillars: (1) optimizing of the patient’s (preoperative) erythrocyte mass, (2) minimizing diagnostic, therapeutic, or intraoperative blood loss, and (3) increasing individual clinician’s tolerance towards anemia and adherence to valid blood transfusion triggers by prudently capitalizing on physiologic tolerance of anemia.16,26

### FUNDAMENTALS OF A PREOPERATIVE ANEMIA MANAGEMENT PROGRAM

A key to achieving such optimal surgery-related patient-centered blood management is a formal preoperative anemia management program (PAMP). Commensurate with the promulgated principles and the above first strategy or pillar of PBM, a formal PAMP primarily identifies surgical patients who are anemic and thus at risk for transfusion and implements a preoperative management plan aimed at reducing or eliminating the presence and/or risk of anemia and the need for allogeneic transfusion, hence reducing the inherent risks, inventory pressures, and the escalating costs associated with transfusion.3,18,26

To this end, a multidisciplinary panel of physicians was recently convened by the Network for Advancement of Transfusion Alternatives with the aim of developing practice guidelines for the detection, evaluation, and management of preoperative anemia (primarily in elective orthopedic surgery) and formulating recommendations using the GRADE working group methodology.16,20 Based upon a systematic literature review and critical evaluation of the evidence, this Network for Advancement of Transfusion Alternatives panel made a series of recommendations (Table 1).

### DEVELOPMENT AND IMPLEMENTATION OF AN ANESTHESIOLOGY-BASED PREOPERATIVE ANEMIA MANAGEMENT PROGRAM

A patient-centered approach to blood management has been advocated by the American Society of Anesthesiologists.31 However, currently, the presence of preoperative anemia is commonly accepted de facto by anesthesiologists. The planned surgery is typically performed as scheduled, without any preemptive corrective action, but instead simply with a lower clinician threshold for intraoperative PRBC transfusion as the default therapy.15,26 This phenomenon is especially noteworthy given the ethical and medico-legal requirement to inform such anemic patients preoperatively on their risks versus benefits with regard to anesthesia and surgery and to plan concomitant diagnostic and treatment measures.18 In order to meet with these requirements, it has been proposed that patients should be initially seen in an outpatient preoperative clinic as soon as possible, but at least three to four weeks before their planned surgery so that appropriate anemia management can be initiated.18 At many institutions (including mine), this hiatus is not feasible, primarily due to a wide patient catchment area and resulting patient inconvenience. This has prompted implementing at our institution a more compressed 12 to 16 day preoperative anemia treatment regimen (Figure 1), which is currently the subject of a prospective conjoint randomized controlled clinical trial and formal health care economic evaluation.

A number of studies have demonstrated the safety and efficacy of the preoperative use of an erythropoietic stimulating agent (ESA) like recombinant human erythropoietin (Table 2), especially in the orthopedic population, for reducing the need for allogeneic red cell transfusion. Of note, the reported side effect profile and adverse event rate (e.g., deep venous thrombosis) in the active treatment versus control groups has been comparable,25,37–46 There is less pain with the subcutaneous injection of epoetin alfa as compared to darbepoetin alfa.47,48 Moreover, epoetin alfa is less expensive and more effective than darbepoetin alfa for an equipotent longitudinal regimen.

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**Table 1. Network for Advancement of Transfusion Alternatives (NATA) recommendations for the detection, evaluation, and management of preoperative anemia.16,20**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GRADE</th>
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<tr>
<td>Elective orthopedic surgical patients should have an Hgb level determination four weeks before surgery, if possible</td>
<td>Grade 1C</td>
</tr>
<tr>
<td>Further laboratory testing for differential diagnosis in those with anemia</td>
<td>Grade 1C</td>
</tr>
<tr>
<td>Nutritional deficiencies should be treated to increasing Hgb before surgery to be within the normal range</td>
<td>Grade 1C</td>
</tr>
<tr>
<td>Erythropoiesis-stimulating agents be used for anemic patients in whom nutritional deficiencies have been excluded, corrected, or both</td>
<td>Grade 2A</td>
</tr>
<tr>
<td>Intravenous iron administration during the preoperative period for patients undergoing orthopedic surgery who are expected to develop severe postoperative anemia</td>
<td>Grade 2B</td>
</tr>
</tbody>
</table>

Hgb: hemoglobin

**Strength of recommendation**: Is risk/benefit clear?

- Yes strong recommendation = Grade 1: “We recommend”
- No weak recommendation = Grade 2: “We suggest”

**Quality of evidence**
- High-quality evidence = A (meta-analyses, randomized controlled trials)
- Moderate-quality evidence = B (randomized controlled trials with limitations, observational studies with large effects)
- Low- or very low-quality evidence = C (observational studies, randomized controlled trials with major limitations)
The United States Food and Drug Administration (FDA) currently requires all ESAs to be prescribed and used under a risk management program, known as a risk evaluation and mitigation strategy, to ensure the safe use of these drugs. The ESAs included in this risk evaluation and mitigation strategy are marketed under the names Epogen®, Procrit®, and Aranesp®. Per the FDA:\footnote{FDA Drug Safety Communication: Erythropoiesis-Stimulating Agents (ESAs): Procrit, Epogen and Aranesp http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200297.htm} “Healthcare professionals who prescribe ESAs for anemia not caused by cancer chemotherapy are required to provide a copy of Medication Guide to each patient or their representative when an ESA is dispensed.” Furthermore: “Healthcare professionals who use ESAs only for non-cancer uses are not required to enroll in the ESA APPRISE Oncology program.”

Patients should receive iron supplementation (Table 3), preferably IV, throughout the presurgical use of an ESA to optimize red blood cell production and to avoid iatrogenic functional iron deficiency.\footnote{20,26,37,49 Large, single, total replacement doses of all parenteral iron preparations (including...} Patients will be monitored for signs and symptoms of hypersensitivity during and after the administration of epoetin alfa and iron sucrose for at least 30 minutes and until clinically stable after completion of the infusion.

Figure 1. Protocol for Preoperative Anemia Management Program (PAMP).
iron sucrose) are conventionally given by IV infusion over one hour.46,50 These high doses have an increased incidence of side effects.30,31 However and alternatively, low doses (100 mg to 200 mg) of iron sucrose have been reportedly given safely as a two-minute slow IV push.51,52 Ferumoxytol can be given over 20–60 seconds.53–56 Iron sucrose was initially approved by the FDA in 2000 and for nondialysis-dependent iron deficiency in 2005. Of note, despite its apparent clinical advantages, ferumoxytol has yet to be FDA approved for treatment of nondialysis-dependent iron deficiency.

The conventional wisdom that surgical patients should be transfused to maintain a Hgb of 10 g/dL and a hematocrit of 30% is no longer valid for most patients.57 Present clinical practice guidelines now recommend restrictive red cell transfusion practices, with the goal of minimizing exposure to allogeneic blood (from an unrelated donor).58 Specifically, the American Association of Blood Banks has recently recommended adhering to a more restrictive transfusion strategy (7 to 8 g/dL) in hospitalized, stable patients (Grade: strong recommendation; high-quality evidence).4

Pertinent to an anesthesiology-based PAMP, a reasonable intraoperative blood conservation protocol applies the same restrictive transfusion trigger (Hgb < 8 g/dL), but also takes into consideration the patient’s intraoperative estimated allowable blood loss and hemodynamic stability. Specifically, if the patient has lost > 30% of his/her estimated blood volume (based upon ideal body weight for height) and requires the administration of an IV medication (vasopressor) for hypotension, the patient will be transfused with 1 (one) unit of PRBCs. Repeat transfusion with PRBCs will occur based on these same criteria. Likewise pertinent to an anesthesiology-based PAMP, consistent with these American Association of Blood Banks guidelines, in postoperative surgical patients, transfusion should be considered at a Hgb concentration of 8 g/dL or less for symptoms of chest pain, orthostatic hypotension or tachycardia unresponsive to fluid resuscitation, or congestive heart failure (Quality of evidence: high; strength of recommendation: strong).4 However, continuous appropriate training, education, and awareness are needed to avoid local guideline-based protocol violations and to limit unnecessary further exposure to allogeneic blood transfusion and its related risks.59

### ROLE OF AN ANESTHESIOLOGY-BASED PREOPERATIVE ANEMIA MANAGEMENT PROGRAM IN A PERIOPERATIVE SURGICAL HOME MODEL

Varied and fragmented care plans, undertaken by different practitioners, currently expose surgical patients to lapses in expected standard of care, increase the chance for operational mistakes and accidents, result in unnecessary and potentially detrimental care, and adversely affect the patient health care experience.59–61 Standardization of perioperative processes is increasingly recognized as needed to optimize not only resource utilization and quality but also patient safety, well-being, and satisfaction.53,63 Likewise, the medical community and the public are increasingly embracing shared decision-making, a process by which health care choices are made jointly by the practitioner and the patient.64,65 Like the Medical Home model that has been implemented in the primary care practice setting,66–68 the Perioperative Surgical Home has thus been proposed by the American Society of Anesthesiologists and other stakeholders as an innovative, patient-centered continuity of care model that emphasizes shared decision-making.69–71 In the Perioperative Surgical Home model, anesthesiologists serve as the surgical patient’s primary perioperativist, providing highly integrated, continuity of care throughout the preoperative, intraoperative, and postoperative periods.71 This broadening of anesthesiologists’ scope of practice should promote such standardization and shared decision-making, thus likely improving clinical outcomes and decreasing unnecessary resource utilization.33,61,71,72 A patient-centered, anesthesiology-based PAMP a logical component of such a multifaceted Perioperative Surgical Home.

While a preanesthetic patient assessment has been a longstanding required element of any anesthetic, it has been historically performed in close proximity to the scheduled surgery and has routinely only collected a limited set of clinical data, including laboratory testing.71 In patients with a greater chronic disease burden, such a perforunctory preanesthetic assessment does not permit the more comprehensive evaluation, or as indicated, a formal consultation, which a more comprehensive Preoperative Assessment, Consultation and Treatment (PACT) Clinic affords.71 The goals of such a PACT Clinic are to identify, to communicate, and whenever possible to minimize the patient-specific, attendant risks of surgery and anesthesia. Logistically, an anesthesiology-based PAMP can be located in such a PACT Clinic, given that preoperative patient optimization readily includes assessment for anemia and the administration of subcutaneous recombinant erythropoietin and IV iron (IV Fe) to reduce or eliminate surgical allogeneic blood transfusions.71

### Table 2. Commercially available erythropoietic stimulating agents (ESA)

<table>
<thead>
<tr>
<th>ESA</th>
<th>Equipotent Dose</th>
<th>Equipotent Dose</th>
<th>Equipotent Dose</th>
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<tbody>
<tr>
<td>Darbepoetin alfa</td>
<td>200 mcg</td>
<td>100 mcg</td>
<td>60 mcg</td>
</tr>
<tr>
<td>Epoetin alfa (Epogen®)</td>
<td>40,000 units</td>
<td>20,000 units</td>
<td>10,000 units</td>
</tr>
<tr>
<td>Epoetin alfa (Procrit®)</td>
<td>40,000 units</td>
<td>20,000 units</td>
<td>10,000 units</td>
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</tbody>
</table>

### Table 3. Contemporary commercially available intravenous iron (IV Fe) preparations

<table>
<thead>
<tr>
<th>IV Fe</th>
<th>Typical lower, split dose, rate of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron sucrose (Venofer®)</td>
<td>100 mg, 200 mg, or 300 mg over 2 to 30 minutes</td>
</tr>
<tr>
<td>Ferric carboxymaltose (Ferinject®)*</td>
<td>500 mg or 1000 mg over 15 minutes</td>
</tr>
<tr>
<td>Ferumoxytol (Feraheme®)**</td>
<td>510 mg in &lt; 60 seconds</td>
</tr>
</tbody>
</table>

*May not be available in the United States

**Approved by the United States Food and Drug Administration in 2009; post-marketing trials continue to be published (but no preoperative data)
BUSINESS MODEL THAT DEMONSTRATES THE COST SAVINGS AND “ADDED VALUE” OF A PREOPERATIVE ANEMIA MANAGEMENT PROGRAM

Minimizing the need for surgical transfusions has not only physiologic but also economic benefits.\(^{20}\) Preoperative treatment of anemia with recombinant human erythropoietin [e.g., epoetin alfa (PROCRIT®), manufactured by Amgen Inc., Thousand Oaks, CA for Janssen Products, LP, Horsham, Pennsylvania] and IV Fe [e.g., iron sucrose (Venofer®), American Regent, Inc., Shirley, NY] have been advocated to reduce the need for allogeneic transfusion.\(^{73,74}\) Such treatment is covered by the Center for Medicare & Medicaid Services and commercial payers (e.g. Blue Cross and Blue Shield).

A retrospective review of University of Alabama Hospital administrative and clinical data from 2011 revealed a cross-sectional 39% prevalence of preoperative non-macrocytic anemia (Hgb ≤ 12.5 g/dL and mean corpuscular volume < 100 fL in females and males) among 358 total hip arthroplasty patients, resulting in 352 PRBC units being transfused in the 128 preoperatively anemic patients (Vetter et al., 2012 American Society of Anesthesiologists Annual Meeting\(^{\circ}\)). Of note, despite receiving a PRBC transfusion, the preoperatively anemic patients had a mean Hgb of 8.8 g/dL (SD 1.1) at time of hospital discharge. The local direct (wholesale) cost of epoetin alfa (PROCRIT®) is $381/ dose (40,000 IU) and the direct (wholesale) cost of iron sucrose (Venofer®) is $63/dose (200 mg), the latter with an estimated administration cost of $50/dose. The estimated total cost of a PRBC unit at University of Alabama Hospital is $1000 ($250 acquisition cost X 4).\(^{28}\) Treating these 128 anemic total hip arthroplasty patients with preoperative ESA + IV Fe therapy (three weekly doses/patient) and postoperative IV Fe (single dose/patient) (applying the protocol in Figure 1) would cost $178,560 versus $352,000 for the estimated total cost of the 352 transfused PRBC units, a net annual savings of $173,440. Further savings would be realized by inclusion of other elective major surgical procedures (e.g. total knee arthroplasty) or if the third dose of epoetin alfa is not needed on the day of surgery.

The Protection and Affordability Care Act of 2010 seeks to reign in spiraling health care costs by fundamentally transforming health care delivery via (a) new care models that deliver more cost-effective and coordinated care and (b) incentive-based reimbursement.\(^{75,76}\) In this new health care paradigm, providers, including anesthesiologists, will be paid not just for the quantity but the quality and value of the services they provide.\(^{71,77,79}\) Value-based purchasing of health care,\(^{70-72}\) pay for performance,\(^{82,83}\) and a changing payment paradigm that includes bundled payments and/or accountable care arrangements\(^{84}\) are all powerful motivators to improve health care delivery and outcomes, particularly in the perioperative setting.\(^{71}\) Hospital-physician collaborations will continue to evolve toward greater economic integration, including major financial gain and risk sharing.\(^{85,86}\) A greater level of payment will be based on


REFERENCES

34. Epstein RM, Fischella K, Lesser CS, Stange KC. Why the nation needs a policy push on patient-centered health care. Health Aff (Millwood) 2010;29:1489–95
38. Goldberg MA. Perioperative epoetin alfa increases red blood cell mass and reduces exposure to transfusions: results of randomized clinical trials. Semin Hematol 1997;34:41–7
46. Auerbach M, Goodnough LT, Picard D, Maniatis A. The role of intravenous iron in perioperative management and transfusion avoidance. Transfusion 2008;48:988–1000


64. Kon AA. The shared decision-making continuum. JAMA 2010;304:903–4


67. Rittenhouse DR, Shortell SM. The patient-centered medical home: will it stand the test of health reform? JAMA 2009;301:2038–40


77. Miller HD. From volume to value: better ways to pay for health care. Health Aff (Millwood) 2009;28:1418–28


86. Trybou J, Gemmel P, Annemans L. The ties that bind: an integrative framework of physician-hospital alignment. BMC Health Serv Res 2011;11:36


Perioperative Antiplatelet Drugs with Coronary Stents and Dancing with Surgeons: Can We Ever Agree About Bleeding Versus Ischemic Risk?

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PHARMACOLOGY OF ANTIPLATELET DRUGS
Aspirin, usually in combination with a thienopyridine (Table 1), is the present-day cornerstone of oral antiplatelet therapy for the prevention of (a) neointimal hyperplasia, with resulting in-stent restenosis and (b) acute stent thrombosis, after placement of a bare-metal stent (BMS) or a drug-eluting stent (DES).1–4 This oral antiplatelet therapy is especially important during the initial critical but often delayed period of reendothelialization of the lumen of the BMS or DES.5,6 Aspirin irreversibly inhibits its platelet cyclooxygenase (COX-1) activity and in turn the synthesis of thromboxane A₂.6 The thienopyridines [e.g., clopidogrel (Plavix®)] irreversibly bind to the platelet P2Y₁₂ receptor and inhibit adenosine diphosphate receptor-mediated platelet activation and aggregation.6 Both aspirin and clopidogrel are “selective platelet-receptor” inhibitors that are considered weaker and thus safe antiplatelet drugs. The co-administration of aspirin and clopidogrel results in enhancement of beneficial platelet inhibition, since they act via the above different platelet receptors.7

Clopidogrel is a pro-drug that must be transformed by the hepatic CYP2C19 isoenzyme into its active metabolite to become clinically effective.7 A reported 1% to 6% of Caucasians, 1% to 8% of African Americans, and 12% to 23% of Asians are CYP2C19 deficient (“poor metabolizers”) and thus at risk of treatment failure.10 A subset of patients also displays diminished or absent response to aspirin (“aspirin resistance”), likely due to a combination of clinical, biological, and genetic properties affecting platelet function.11 This has raised the concern of drug resistance, with both clopidogrel and aspirin, which has been associated with an increased risk of an acute thrombotic event.12,13 This is problematic because while there is commercially available CYP2C19 clinical genotyping,14,15 there is no readily available, reliable laboratory measure of platelet function.13,16

The proton-pump inhibitors, omeprazole (Prilosec®) and esomeprazole (Nexium®) are also hepatically metabolized by CYP2C19. Omeprazole and esomeprazole compete with clopidogrel for the CYP2C19 isoenzyme, thus decreasing the conversion of clopidogrel into its clinically active metabolite and possibly reducing its cardioprotective effect.17,18 This drug-drug interaction prompted the United States Food and Drug Administration (U.S. FDA) in November 2012 to issue a safety labeling change, warning against the concomitant use of esomeprazole or omeprazole with clopidogrel.19

While clopidogrel and ticlopidine (Ticlid®) are metabolized solely by the hepatic cytochrome P450 system, prasugrel (Effient®) is also converted to its active thiolactone by carboxylesterase 2 hydrolysis during its intestinal absorption, resulting in a reportedly more predictable antiplatelet effect with prasugrel.20–22 Ticagrelor (Brilinta®) is a distinct cyclo-pentyl-triazolo-pyrimidine, which binds reversibly, and directly without biotransformation, to the P2Y₁₂ receptor on platelets.23,24,25 Cangrelor is an IV-administered cyclo-pentyl-triazolo-pyrimidine, with rapid onset and return of normal platelet function within 60 minutes of discontinuation, which is currently awaiting U.S. FDA approval.26,25

Of note, given the rapid onset of action of prasugrel or ticagrelor and their potential to decrease the risk of acute stent thrombosis, current international guidelines recommend prasugrel and ticagrelor in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention (PCI).24–26 However, in June 2009, the European Medicines Agency authorized six generic versions of clopidogrel, and in May 2012, the U.S. FDA approved generic clopidogrel. The net effect of these available generics on the previously dominant worldwide market share of proprietary Plavix® remains to be determined. Ultimately, the clinical benefits associated with prasugrel and ticagrelor need to be offset against their increased cost, promoting the need for an algorithm for using these new drugs in the primary PCI setting.27

PATHOPHYSIOLOGY AND EPIDEMIOLOGY OF A PERIOPERATIVE MAJOR CARDIAC ADVERSE EVENT WITH CORONARY ARTERY STENTS
With the advent of PCI, in particular, coronary artery stenting, interventional cardiology has made significant progress in the management of coronary artery disease.5 The scope of interventional cardiology has also greatly increased with the development of the BMS and DES (Table 2), and the associated use of antiplatelet drugs.2

While such strategies have reduced the need for more invasive coronary artery bypass grafting (CABG) surgery, a major adverse cardiac event (MACE) can occur after coronary artery stent placement. While the definition of a MACE has varied considerably and hence the validity of such a composite end point in cardiovascular studies has been questioned,2 in patients who have undergone a PCI, a MACE conventionally includes any of the following:

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Clinical and angiographic risk factors for 64% incidence of death or MI at the time of acute stent angiographic-confirmed stent thrombosis has a reported stent deployment, and current antithrombotic regimens, the modern era of second-generation stents, high-pressure stent placement) have been well-defined4,5,28,32 to include:

- Death from all causes
- Q-wave and non-Q-wave myocardial infarction (MI)
- Coronary artery stent thrombosis and occlusion
- Target vessel restenosis
- Target lesion revascularization
- CABG
- Stroke

Specifically, acute coronary artery stent thrombosis and occlusion carries a very high morbidity and mortality.2,5 In the modern era of second-generation stents, high-pressure stent deployment, and current antithrombotic regimens, angiographic-confirmed stent thrombosis has a reported 64% incidence of death or MI at the time of acute stent thrombosis.31 Clinical and angiographic risk factors for early stent thrombosis (within 30 days of initial stent placement) and late stent thrombosis (LST) (> 30 days after initial stent placement) have been well-defined4,5,28,32 to include:

- Premature discontinuation of antiplatelet therapy
- Advanced age (> 75 years)
- Acute coronary syndrome (at the time of initial stent placement)
- History of coronary artery stent thrombosis
- Diabetes (poorly controlled with a hemoglobin A1C > 9.0)
- Low ejection fraction (left ventricular ejection fraction < 30%)
- Anemia (with hemoglobin < 10 g/dL)
- Chronic renal insufficiency (creatinine > 2.0 mg/dL)
- Prior brachytherapy for prostate or cervical cancer
- Stent in left main artery, proximal left anterior descending, proximal right coronary artery, or proximal dominant circumflex artery
- Long stents, multiple, or overlapping stents in a single vessel
- Ostial or bifurcation lesions
- Post-CABG stent(s) in saphenous vein graft(s)

A0–19 point scoring system for risk of LST (low, medium, high, very high) has been developed.3,28 However, several studies have identified the most important risk factor for LST is the complete and premature discontinuation of dual antiplatelet therapy.28,32

Perioperative coronary artery stent thrombosis is likewise a catastrophic, often life-threatening complication that can occur in patients with either a BMS or DES.5,30,33–35 Noncardiac surgery appears to increase the risk of acute stent thrombosis, myocardial ischemia and MI, and death, especially when patients undergo surgery soon after stent implantation.29,36 The incidence of these complications is further increased when dual-antiplatelet therapy is abruptly discontinued preoperatively39,40. This is likely due to a “rebound hypercoagulability” that lasts upwards of 90 days after such abrupt cessation of antiplatelet therapy.39,40 This rebound is marked by an inflammatory prothrombotic state, increased platelet adhesion and aggregation, and excessive thromboxane A2 activity.37,41,42 Surgery itself further promotes an inflammatory response and prothrombotic state, which, in the presence of an incompletely reendothelialized DES, can lead to an acute stent thrombosis, with likely MI and/or death.37,41,42

In one Mayo Clinic study, the incidence of a MACE was reportedly lowest when noncardiac surgery was performed at least 90 days after PCI with BMS placement, but remained at 2.8% thereafter.34 In a concomitant Mayo Clinic study, the risk of a MACE with noncardiac surgery after DES placement was observed to not be significantly associated with time between stenting and surgery, but the observed MACE rates were lowest after 365 days, but

### Table 2. Currently U.S. Food and Drug Administration (FDA) approved bare-metal stents (BMS) and drug-eluting stents (DES)26,29

<table>
<thead>
<tr>
<th>Stent (manufacturer, FDA approval date)</th>
<th>Generation</th>
<th>Type of stent</th>
<th>Drug eluted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liberté* (Boston Scientific)</td>
<td>First</td>
<td>BMS: 316L Stainless steel</td>
<td>N/A</td>
</tr>
<tr>
<td>VeriFLEX* (Boston Scientific)</td>
<td>First</td>
<td>BMS: 316L Stainless steel</td>
<td>N/A</td>
</tr>
<tr>
<td>Bx Velocity (Cordis/J&amp;J)</td>
<td>First</td>
<td>BMS: 316L Stainless steel</td>
<td>N/A</td>
</tr>
<tr>
<td>Vision (Abbott)</td>
<td>Second</td>
<td>BMS: Cobalt chromium</td>
<td>N/A</td>
</tr>
<tr>
<td>Driver/Integrity (Medtronic)</td>
<td>Second</td>
<td>BMS: Cobalt chromium</td>
<td>N/A</td>
</tr>
<tr>
<td>Omega (Boston Scientific, trials underway)</td>
<td>Third</td>
<td>BMS: Platinum Chromium</td>
<td>N/A</td>
</tr>
<tr>
<td>Cypher (Cordis, 4/2003)</td>
<td>First</td>
<td>DES: 316L Stainless steel</td>
<td>Sirolimus</td>
</tr>
<tr>
<td>Endeavor (Medtronic, 2/2008)</td>
<td>Second</td>
<td>DES: Cobalt chromium</td>
<td>Zotarolimus</td>
</tr>
<tr>
<td>Promus (Medtronic-marketed Xience)</td>
<td>Second</td>
<td>DES: Cobalt chromium</td>
<td>Everolimus</td>
</tr>
<tr>
<td>Promus Element (Medtronic, 11/2011)</td>
<td>Third</td>
<td>DES: Platinum chromium</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>Taxus Ion (Boston Scientific, 2/2012)</td>
<td>Third</td>
<td>DES: Platinum chromium</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>Resolute (Medtronic, 2/2013)</td>
<td>Third</td>
<td>DES: Cobalt chromium</td>
<td>Zotarolimus</td>
</tr>
</tbody>
</table>

*Liberté BMS was renamed VeriFLEX BMS by Boston Scientific in late 2009, to prevent continued confusion and inadvertent implantation of Taxus Liberté DES and vice versa.
remained at 3.3% thereafter. Subsequent analyses of large-scale Canadian patient registry data and population-based administrative health care databases have revealed the earliest optimal time for elective surgery is 46 to 180 days after BMS implantation and 180 days after DES implantation. However, in a cohort of Dutch noncardiac surgery patients who experienced a MACE, 45% were receiving single and 55% receiving dual antiplatelet therapy. So indeed it would appear that “timing is everything,” at least with elective noncardiac surgery in patients with a coronary artery stent.

**RISK OF INTRAOPERATIVE AND POSTOPERATIVE SURGICAL BLEEDING WITH ANTIPLATELET DRUGS**

In the above two Mayo Clinic studies on the optimal timing of noncardiac surgery after BMS and DES placement, the continuation of dual antiplatelet therapy at the time of surgery did not increase the risk of major surgical bleeding. However, in the above Dutch study of the optimal timing of noncardiac surgery versus stent placement, the risk of severe, life-threatening bleeding (defined as fatal bleeding, intracranial bleeding, or bleeding requiring surgical intervention or transfusion of ≥ 4 units of blood or blood products) was reported to be 4% with single antiplatelet therapy and 21% with dual antiplatelet therapy.

Based upon an extensive review of the available literature, after excluding cardiac surgery (with full intraoperative heparinization for cardiopulmonary bypass), surgical blood loss is increased 2.5% to 20% by aspirin alone, and 30% to 50% by aspirin and clopidogrel, but with no increased risk of bleeding-related mortality except during intracranial surgery. Of note, transfusion rates are reportedly increased by 30% with continuation of dual antiplatelet therapy at the time of surgery.

It is generally felt that antiplatelet therapy (aspirin and/or clopidogrel) should be continued throughout the perioperative period, except in cases where the risk of morbidity and mortality from bleeding during and after surgery significantly outweighs the risk of acute stent thrombosis, as with procedures likely to be associated with major (massive) blood loss or performed in a closed space (e.g. intracranial, intraspinal, posterior eye chamber, transurethral prostatectomy). While the latter circumstances are frequently quite evident, the former is often more subjective and hence ambiguous.

Current Evidence and Guidelines for the Perioperative Management of Antiplatelet Drugs in Patients with a Coronary Artery Stent

The optimal perioperative management of patients with a coronary artery stent hence remains a very significant yet challenging patient safety issue for clinicians. The U.S. FDA and the American Heart Association/American College of Cardiologists have recommended continuing dual-antiplatelet therapy in patients with a DES for one year and in patients with a BMS for six weeks. Unless medically contraindicated, all patients with any type of coronary artery stent should remain on life-long aspirin monotherapy. These therapies for the prevention of stent thrombosis have major implications for anesthesiologists and surgeons. Not surprisingly, these recommendations regarding the optimal duration of and perioperative continuation of antiplatelet therapy continue to be debated, both in the literature and in routine clinical practice. Hence the title of this paper, “Dancing with Surgeons: Can We Ever Agree about Bleeding versus Ischemic Risk?” The answer is likely yes; though despite the availability of the above published clinical practice guidelines, “all politics is local.”

**PRINCIPLES AND USE OF CONSENSUS DECISION-MAKING**

Consensus decision-making is one form of group decision making. Consensus decision-making does not require unanimity but instead seeks the agreement of the majority of participants as well as the resolution or mitigation of minority held objections. Consensus decision-making is applicable to the management of complex clinical conditions, in particular, the development of clinical practice guidelines and clinical care pathways, involving a variety of health care providers.

Specifically, the Consensus-Oriented Decision-Making (CODM) model has been successfully applied to arrive at a consensus among local clinical stakeholders about the management of patients with coronary artery stents. Offering a detailed, step-wise description of the consensus process, the CODM model can be applied in any type of decision-making process. It outlines a process in which proposals can be collaboratively built with full participation of all stakeholders. The CODM model allows groups to be flexible enough to make decisions when they need to, while still following a format that is based on the primary values and goals of consensus decision-making. The CODM model involves seven steps:

- Framing the topic
- Open Discussion
- Identifying Underlying Concerns
- Collaborative Proposal Building
- Choosing a Direction
- Synthesizing a Final Proposal
- Closure

**ACHIEVING INSTITUTIONAL STAKEHOLDER CONSENSUS ABOUT PERIOPERATIVE ANTIPLATELET DRUGS FOR CORONARY ARTERY STENTS**

Coordinated care by all clinicians involved with a coronary artery stent patient is essential to avoid a high incidence of perioperative cardiac mortality and morbidity. Currently, though, as noted above, there are limited published data to guide surgeons, anesthesiologists, cardiologists, and primary care physicians, on the optimal care of patients with indwelling coronary artery stents presenting for noncardiac surgery. Surgery on a patient receiving antiplatelet therapy thus creates a dilemma: Is it better to withdraw the drugs and reduce the hemorrhagic risk or to maintain them and reduce the risk of a myocardial ischemic event? In either case, optimal perioperative care includes prompt recognition of myocardial ischemia and/or infarction. If stent thrombosis occurs, rapid triage to an interventional catheterization laboratory is essential for restoration of coronary blood flow.
From July 2011 to November 2011, the above seven-step CODM model was followed to arrive at a consensus, among the institutional clinical stakeholders at the University of Alabama at Birmingham Health System (UABHS), and to develop a protocol for the perioperative management of patients with indwelling coronary artery stent(s) undergoing elective surgery at our satellite university hospital without an on-site cardiac catheterization laboratory.60 Subsequently, between January 2013 and March 2013, this CODM model was also reiteratively applied by a UABHS Anticoagulation Task Force to create two evidence-based and local expert opinion-supported protocols (Figure 1A and Figure 1B), which standardized the preoperative management of antiplatelet therapy in patients with an indwelling coronary BMS or DES. This small yet multidisciplinary clinical task force included representatives from anesthesiology, cardiology, critical care medicine, gynecology, hospitalist medicine, pulmonology, transfusion medicine, and surgery. The efforts of this task force were enhanced the well-established UAB Department of Anesthesiology Section on Quality and Patient Safety55 and the departmental electronic Anesthesiology Dashboard, TM which provided an online mechanism for efficient sharing of pertinent published articles and successive protocol drafts.

1. Determine whether it would have been indicated, based on the BMS protocol or DES protocol, for the patient to stop single or dual antiplatelet therapy.

2. If discontinuation of the antiplatelet drug and/or aspirin is indicated by the protocol, surgery may proceed as planned.

3. If continuation of aspirin is indicated per the protocol, and the patient has been off aspirin for more than 5 days: (a) if there is a high risk of morbidity or mortality from bleeding during and after the planned procedure, obtain cardiology consult for management recommendations; (b) if there is an intermediate risk from bleeding during and after the planned procedure, give 81 mg of aspirin before surgery; and (c) if there is low risk of morbidity or mortality from bleeding during and after the planned procedure, give 325 mg of aspirin before surgery.

4. If continuation of another antiplatelet drug (other than aspirin) is indicated by the protocol, and the patient has been off this drug for more than 5 days, options include:
   a. Give 600 mg of clopidogrel and proceed with surgery a minimum of 2 hours later.
   b. Give 300 mg of clopidogrel and proceed with surgery a minimum of 4 hours later.
   c. Reschedule surgery for a later date. In this case, give 300 mg of clopidogrel and start clopidogrel 75 mg daily.
   d. If there is a high risk of morbidity or mortality from bleeding during and after the planned procedure, obtain Cardiology consult for management recommendations.

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Figure 1A. Protocol for preoperative antiplatelet therapy with an indwelling bare metal stent (BMS) (See "*Day of Surgery Proviso" below)1,3,28,34,36,37,42–45,47–50,52,62,63,66–91
REFERENCES

9. Cheng X, Chen WH, Simon DI. Aspirin resistance or variable response or both? Am J Cardiol 2006;98:11N–7N

Figure 1B. Protocol for preoperative antiplatelet therapy with an indwelling drug-eluting stent (DES) (*See “Day of Surgery Proviso” below)1–5,28,32–38,42–50,52,62–64,66–132

*Day of Surgery Proviso: For patients scheduled for elective surgery who have independently stopped antiplatelet therapy before presentation to UAB on the day of surgery, the following steps can be used to guide the joint decision making by the anesthesiologist and surgeon.


29. Cutlip D, Abbott JD. Drug-eluting compared to bare metal intracoronary stents UpToDate. Waltham, MA: UpToDate, 2013.


85. Servin FS. Is it time to re-evaluate the routines about stopping/keeping platelet inhibitors in conjunction to ambulatory surgery? Curr Opin Anaesthesiol 2010;23:691–6

86. Singh S, Sachdeva R, Uretsky BF. The risk of adverse cardiac and bleeding events following noncardiac surgery relative to antiplatelet therapy in patients with prior percutaneous coronary intervention. J Am Coll Cardiol 2012;60:2005–16


