Review Course Lectures
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Thoracic Endovascular Aortic Repair (TEVAR): Perioperative Management and Outcomes

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OBJECTIVES
1. To review the pathophysiology of descending thoracic aortic disease
2. To discuss the perioperative management and anesthetic considerations in TEVAR surgery
3. To review the postoperative outcomes of descending Thoracic Endovascular Aortic Repair

SUGGESTED READINGS:
Transfusion-related Acute Lung Injury

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OBJECTIVES

Objectives of this lecture will be 1). To review recent data on the prevalence of transfusion-related acute lung injury (TRALI), 2). To examine proposed mechanisms for the development of TRALI and 3). To provide data on lung injury as it relates to red cell and component transfusion.

Transfusion-related acute lung injury (TRALI) is the most common cause of morbidity related to transfusion. Contemporary data from the Food and Drug Administration FY 2009 reports TRALI is the most frequent cause of transfusion-related mortality in the US. Blood components containing plasma have been implicated in TRALI with fresh frozen plasma (FFP), and red blood cell (RBC) units the most commonly implicated products. A recent publication noted that residual plasma in amounts as little as 10-20ml that contain donor derived white blood cell antibodies can cause TRALI.

Clinically TRALI is characterized by acute onset of respiratory distress, accompanied by hypoxemia, bilateral infiltrates on CXR, and presenting within 6 hours of transfusion. In addition, there should be no evidence of left atrial hypertension and a lack of temporal relationship to alternative risk factor for acute lung injury. Reports note that over 70% of patients may require mechanical ventilation to support oxygenation however a majority will have symptom resolution within 96 hours.

Two most commonly proposed mechanisms for the development of TRALI include the immune-mediated theory and the two-hit hypothesis. The immune-mediated theory proposes that TRALI develops as a result of a passive transfer of HLA or HNA antibodies from the donor product that react against the recipients leukocyte antigen resulting in activation of the recipient leukocytes, with release of cytotoxic contents and subsequent pulmonary microvascular lung injury. Approximately, 60-90% of reported TRALI cases have been attributed to the immune-mediated TRALI theory.

The second theory for development of TRALI is the two-hit model whereby a ‘first hit’ or inciting event, such as surgery or trauma, primes the patient’s neutrophils and activates the pulmonary endothelial cells leading to pulmonary sequestration of neutrophils. The ‘second hit’ occurs with transfusion of biologically active mediators present in the blood product. As a consequence of the ‘second hit’ the neutrophils become activated, releasing their cytotoxic contents with resultant pulmonary endothelial cell damage.

Women who have become pregnant frequently have HLA antibodies with prevalence estimates ranging from 27-30% for women who have had 3 or more pregnancies. (Prevalence of antibodies increase with increasing number of pregnancies). Elimination of female plasma donors has been implemented to mitigate the risk of TRALI. In the US approximately 95% of plasma is from male donors; for more rare blood types approximately 65% is from male only donors. As noted, the diagnosis of TRALI is primarily a clinical one and is particularly challenging in the surgical setting. Education and improved surveillance will allow for adequate diagnosis and more accurate prevalence estimates.

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Lies, Damned Lies & Anesthesia Myths

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INTRODUCTION

Physicians, journalists, scientists and the lay public prefer a plausible narrative (particularly if it includes mechanistic details) to being forced to acknowledge that “I don’t know” or “the data are suggestive but inconclusive.” The inevitable result is that unproven hypotheses, repeatedly endlessly in lectures and textbooks and assumed to be facts, become part of the canon of the specialty. Whether these misapprehensions be “lies, damned lies, and statistics,” using a turn of phrase that Mark Twain attributed to Benjamin Disraeli (erroneously) in Twain’s Chapters from My Autobiography, or whether they be “anesthesia myths” I will leave to the reader/listener to decide.¹

We will consider a representative subset of unproven (and, in some cases, disproven) hypotheses during the course of this brief presentation. For convenience, I have divided the topics into two classes: those related to general anesthesia and those related to regional anesthesia.

GENERAL ANESTHESIA

Cricoid pressure improves patient safety

Cricoid pressure was introduced to anesthesia by Brian Sellick article in 1961.² In 26 patients considered at risk for aspiration, no regurgitation occurred before or after application of cricoid pressure in 23. In 3 patients, regurgitation occurred after cricoid pressure was relieved following tracheal intubation. The assumption was that cricoid pressure prevented regurgitation from occurring prior to and during intubation in these 3 patients. But, Sellick did not provide details of induction drugs, ventilation, patient body habitus, or other relevant factors that might also explain differences between the two groups.³ Sellick assumed that the cricoid cartilage, esophagus, and anterior surface of the vertebral body would be in consistent anterior to posterior alignment. He presumed that his maneuver would fully occlude the esophagus, would prevent gastric contents from refluxing past the cricoid, and thus would reduce the incidence of pulmonary aspiration associated with “full stomach” conditions. Finally, he assumed that cricoid pressure had no adverse consequences. Current data using CT and MR imaging techniques confirm that the cricoid, esophagus, and vertebral body are not in consistent alignment and cricoid pressure does not consistently occlude the esophagus. Small studies in animals and cadavers demonstrate that cricoid pressure prevents reflux of water injected at increased pressure into the esophagus, but there are no human studies on this phenomenon.⁴ There are no outcome studies showing a reduced incidence of aspiration with use of cricoid pressure, but such studies would not be feasible given rates of aspiration during emergency surgery of 1 per 1000 or less. As for adverse effects of cricoid pressure, multiple studies have shown that it can worsen the clinician’s view of the airway during direct laryngoscopy.⁵ 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.⁶ Curiously, cricoid pressure is regarded as standard of care by many.

Invasive monitoring yields a more hemodynamically stable induction

Many books and many clinicians emphasize the importance of placing hemodynamic monitors before induction of general anesthesia. But is there any evidence that having information from a pulmonary artery catheter improves 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.⁷ Moreover, placement of an introducer sheath and 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 improves outcomes.⁸

A slow, careful cardiac induction is preferable

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 intravenous fluid boluses than a slower (2 min) opioid-relaxant induction or a very slow, careful (5-10 min) opioid-relaxant induction.⁹¹⁰

REGIONAL ANESTHESIA

pKa predicts speed of onset of regional anesthesia

All local anesthetic compounds (with the exception of 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.¹¹ It has long been assumed that when...
two local anesthetic compounds are compared for speed of onset, the compound with the reduced pKa will be the faster one, because after injection, a greater 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 than bupivacaine and lidocaine has a faster onset. But, chloroprocaine has the largest pKa of all and it has the fastest onset of all, 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 agents.

Methemoglobinemia and prilocaine

Methemoglobinemia has long been linked to prilocaine, the only local anesthetic that is metabolized to o-toluidine. According to textbooks, prilocaine will reliably produce medically important degrees of methemoglobinemia when doses >600 mg are administered. Recent work by Vasters and colleagues suggests that serious degrees of methemoglobinemia can be associated with prilocaine doses as small as 400 mg in fit adult patients. Interestingly, in another recent study, the local anesthetic most commonly associated with serious degrees of methemoglobinemia was benzocaine.

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. The suggestion was made (and reinforced in an ASRA 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? In fact, large series of interscalene blocks performed in patients receiving general anesthesia report an incidence of adverse neurologic events no different from that reported in large series of interscalene blocks performed without general anesthesia. In the absence of evidence, and based only case reports, is it reasonable to issue a practice guideline that, in effect, labels the use of deep sedation or general anesthesia before interscalene block as malpractice?

CONCLUSIONS

There are a great many accepted practices and published statements in anesthesia that are not supported by strong data sets. In some cases, the available data contradict the prevailing opinion. Although there is little evidence that out and out lies are being promulgated knowingly, it is clear that myths and unproven hypotheses continue to masquerade as received knowledge in our specialty.

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Pediatric Airway Management:
Congenital Anomalies that Can Make Your Life Difficult!

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Congenital anomalies in children can be devastating to the families as well as the infants. Most of these congenital anomalies are diagnosed intrauterine and the anticipation for these difficulties are usually recognized well in advance of the delivery. However, there are some anomalies, which lead to greater difficulty in later life especially as the child is growing. We will discuss in this refresher course common congenital anomalies that lead to potential difficulties in airway management either in emergencies or in an elective setting. In the perioperative cardiac arrest database (POCA), it was noted that airway and respiratory compromise lead to greater number of perioperative cardiac arrest in children.\(^1\)

There are 3 major areas of compromise with airways
(i) Difficult airway with potential syndromes etc that lead to an inability to conventionally ventilate or intubate by skilled practitioners.
(ii) Difficult ventilation with an inability to maintain oxygen saturation due to potential difficulty in maintaining a good mask airway and
(iii) Difficult intubation with an inability to intubate with a minimum of 3 attempts using different techniques.

Common airways changes in children: The tongue is larger in relation to the oral cavity; the epiglottis is large and floppy making it difficult to visualize the airway. The larynx is located higher in infants than in adults hence requiring a straight blade to intubate; the cricoid is the narrowest portion in an infant and hence larger endotracheal tubes may lead to airway compromise. In addition, infants have large heads with an inability for them to breathe through their mouths being obligate nasal breathers. It is then imperative to understand that if there is obstruction to the nasal passages, these infants may not be able to maintain their airway. We will discuss common congenital anomalies that lead to airway obstruction or difficulties in children. It is important to get a good history including potential difficulties in intubation with previous anesthetics, radiological evaluation of the neck if available and examination of the airway including checking the Mallampati score for airway intubation ease. After a brief description of the airway anomalies, we will then describe methods for securing the airways.

Pierre Robin sequence: The characteristic presentation is a combination of mandibular hypoplasia, glossoptosis and possible cleft palate. These infants have a potential for airway obstruction and potential hypoxic injury. It is imperative to secure an airway in the best possible clinical setting possibly in an operating room setting with an option for emergency airway access in the event there is difficulty. Options will be discussed in the section below.\(^2\)

Treacher Collins Syndrome: This is a syndrome which may present at birth with difficulty in airway access and respiratory distress. The syndrome is characterized by mandibular hypoplasia, sunken eyes, large nose and deformity of the ears with microtia being a common associated abnormality. Occasionally they may be associated with a choanal atresia. These children usually come in for major plastic surgery procedures that require airway intervention.\(^3\) (Figure-1)

Goldenhar syndrome: Another anomaly that involves facial asymmetry due to mandibular hypoplasia, prominent forehead, hypoplasia of the zygomatic region and a receding chin. They present for mainly plastic surgery procedures that may require airway intervention.\(^4\)

Hurlers & Hunters syndrome: This is an autosomal recessive mucopolysaccharide storage disease. It leads to development of facial dysmorphism, short stature, dementia and corneal clouding. This also leads to progressive airway obstruction. Children usually require anesthesia for central line placement or for imaging of their spine or airway.\(^5\) (Figure-2)

There are other common syndromes including Down’s syndrome patients who may have airway compromises especially larger tongues, smaller airway diameter which may lead to obstruction on induction of anesthesia.

Equipment: It is essential that the practitioner have several laryngoscope blades including straight blades, and curved blades of various sizes. In addition the use of an oxiscope, a laryngoscope blade with the ability for oxygen to be delivered while performing a laryngoscopy can be of additional help. Additional equipment including laryngeal mask airways, fiberoptic scopes as well as other airway instrumentation devices are important to have expertise on prior to attempting a difficult intubation. It is also important to remember the fact that airway instrumentation after multiple attempts especially with an optical device can be very difficult. A full description of all the available airway devices will be provided in the lecture.
The ASA difficult airway algorithm is used for all difficult airways and can be used effectively in children. The suggested method that we use in our practice is as follows:

1. Reposition patient and try to access the airway using a different blade (straight blade)
2. Place LMA to facilitate airway access. The use of the AirQ LMA has been demonstrated in our experience to facilitate easier access to the airway in children.
3. Attempt to intubate using the LMA as a conduit.
4. If this fails then attempt direct fiberoptic intubation.
5. Cricothyrotomy or tracheostomy if needed.

In addition to the above steps, it is important to keep in mind that each scenario is different and may necessitate a different modality of access to the airway.

**CONCLUSION**

Pediatric airway emergencies due to congenital anomalies can be devastating and difficult to manage. A concerted effort to use judgment prior to anesthetizing infants and children and to use available technology to secure an airway can be rewarding. Careful evaluation of the patient’s history and performing an adequate physical exam is crucial in securing the airway.

**REFERENCES**

Coagulation Cocktails: Helpful Hints and Hard Data for Perioperative Bleeding

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INTRODUCTION

Patients in a perioperative setting often receive anticoagulation for multiple reasons that include atrial fibrillation and ischemic cardiovascular disease. In patients with an acute coronary syndrome, following percutaneous coronary interventions, or with an acute ischemic stroke, the rupture or injury of an atherosclerotic arterial plaque serves as a nidus for platelet aggregation and thrombus formation, which, in turn, may cause myocardial infarction, stroke, or death. Activation and expression of the glycoprotein IIb/IIIa receptor (where fibrinogen binds) on platelets leads platelet aggregation and, thrombus formation. When this receptor is activated, circulating fibrinogen binds to it and cross-links with adjacent platelets to create a platelet–fibrinogen matrix. Since platelets have a pivotal role in the pathogenesis of thrombosis after plaque rupture, antiplatelet agents including aspirin, thienopyridines (clopidogrel, prasugrel, ticagrelor), and the glycoprotein IIb/IIIa inhibitors, reduce adverse events that are associated with plaque rupture.

As a result, patients often present for surgery with underlying hemostatic disorders because of preexisting preoperative anticoagulation or antiplatelet therapy. Patients may also present receiving anticoagulation therapy for reasons that include atrial fibrillation, venous thrombosis prophylaxis, prosthetic valves, or for coronary artery disease. All therapies that prevent clot from forming in pathologic states, also interfere with normal hemostasis, an important mechanism to protect patients from exsanguination.

OVERVIEW OF HEMOSTASIS

Hemostasis is also a far more complex system than intrinsic and extrinsic hemostatic activation as taught in medical school. Multiple factors are responsible for stopping bleeding including release of tissue factor, and generation of factor VIIa, platelet activation, and the complex cellular and humoral amplification that follows. There is a complex equilibrium between blood cells, platelets, coagulation factors, natural inhibitors of coagulation, and the fibrinolytic system. Surgical patients will develop acquired hemostatic changes that contribute to postoperative bleeding that include activation of the coagulation, fibrinolytic, and inflammatory pathways. Even healthy patients can develop coagulopathy following massive hemorrhage and/or tissue injury following trauma, surgery, or in an obstetrical population.

The increasing use of low-molecular weight heparins (LMWH), oral anticoagulants (warfarin and new oral agents rivaroxaban and dabigatran), platelet inhibitors (thienopyridines-clopidogrel, prasugrel or ticagrelor), or direct thrombin inhibitors (r-hirudin, bivalirudin, argatroban), also may potentiate bleeding. This review will focus on current pharmacologic anticoagulation therapies surgical patients may receive and therapeutic perioperative and prohemostatic pharmacologic approaches that are used to treat or prevent bleeding in this setting.

ANTICOAGULATION

Anticoagulation is based on inhibiting both thrombin activation and platelet activation. Thrombin is a potent procoagulant that generates fibrin from soluble fibrinogen, activating factors V and VIII, and activating platelets. Activated platelets adhere to injured vascular endothelia, express IIb/IIIa receptors, aggregate, and further increase generation of thrombin. Because of the complex humoral amplification system linking both hemostatic and inflammatory responses, there are multiple pathways to produce thrombin and prothrombotic effects. Anticoagulation is based on inhibiting both thrombin activation and platelet activation. Thrombin is a potent procoagulant that generates fibrin from soluble fibrinogen, activating factors V and VIII, and activating platelets. Activated platelets adhere to injured vascular endothelia, express IIb/IIIa receptors, aggregate, and further increase generation of thrombin. Current and future anticoagulants used to prevent clot formation will be considered.

HEPARIN

Heparin, the most commonly used anticoagulant, is isolated from porcine intestine where it is stored in the mast cell granules. Unfractionated heparin (UFH) is a diverse mixture of 3000 to 30,000 dalton fragments. Heparin binds to antithrombin III (also called antithrombin or AT) increasing the rate of thrombin–AT III complex formation, but also inhibits other steps in coagulation. Advantages of heparin anticoagulation is that it can be reversed immediately by protamine and has a relatively shorter half life compared to other agents. UFH is also an important cause of heparin induced thrombocytopenia that can occur ~1-3% of patients who receive it.

LOW-MOLECULAR-WEIGHT HEPARINS (LMWH)

Like UFH, low-molecular-weight heparins (LMWHs) are glycosaminoglycans purified from UFH to a molecular weight ~5000. LMWHs have a longer half-life, and in patients with renal dysfunction, the effects can be greatly prolonged and should be avoided.
in this setting. Commonly used LMWHs include enoxaparin and dalteparin, and generic agents will be available soon.

**SYNTHETIC XA INHIBITORS (FONDAPARINUX)**

Fondaparinux is a synthetic antithrombotic agent with specific antiXa activity. Its pharmacokinetic properties allow for a simple, fixed-dose, once-daily regimen of subcutaneous injection, without the need for monitoring. This agent also has a long half life and should be avoided with renal dysfunction.24

**ORAL ANTIICOAGULANTS:**

**Vitamin K Antagonists: Warfarin**

Warfarin has been the only oral agent available until recent approval of new agents that follow. Disadvantages of warfarin include delayed onset of action, the need for routine laboratory monitoring, difficulty in reversal should a surgical procedure create concern about bleeding.25 Warfarin inhibits an enzymatic process of vitamin K epoxide reductase that converts the vitamin K-dependent coagulation proteins (factors II (prothrombin), VII, IX, and X) to their active form. A posttranslational modification and as a result warfarin is called a vitamin K antagonist (VKA). Peak effects of warfarin do not occur for 36 to 72 hours because of its mechanism of action.25

**Warfarin Management Before Elective Surgery**

In patients receiving warfarin, the INR should be checked preoperatively. Although minor surgical procedures can be safely performed in patients receiving oral anticoagulants, for major surgery, discontinuation of oral anticoagulants preoperatively is recommended. Patients with prosthetic heart valves will often require bridging with UFH.25 Bleeding is the main complication of any anticoagulant therapy. Vitamin K will not immediately reverse the anticoagulant effect and additional therapies are needed as detailed in the guidelines for perioperative management by Douketis in the ACCP guidelines and summarized as follows in Perioperative Management of Antithrombotic Therapy.26

**NEW ORAL AGENTS: DABIGATHIN AND RIVAROXABAN**

The newer oral agents have a rapid onset with therapeutic anticoagulation within hours of administration and do not require routine monitoring. Dabigatran is an oral direct thrombin inhibitor, and rivaroxaban is a direct factor Xa inhibitor similar to low molecular weight heparin but independent of ATIII.24 Both of the newer agents require dose adjustments for renal failure and will be considered separately, along with agents under investigation.24,27

**Dabigatran Eteixilate (Pradaxa)**

Dabigatran etexilate is an oral, direct thrombin inhibitor approved for the prevention of stroke with atrial fibrillation that has a rapid onset of action, no requirement for routine coagulation monitoring, and approved outside of the US for the prevention of VTE after total hip or knee replacement surgery. Dabigatran’s effects can be measured best by thrombin times and also by aPTT values, although thrombin times are preferred.25 Dosing should also be adjusted for patients with renal dysfunction.

**Rivaroxaban (Xarelto)**

Rivaroxaban is an oral, direct Factor Xa inhibitor that dose not require antithrombin as a co-factor. Direct Factor Xa inhibitors, including rivaroxaban, apixiban, and edoxaban can inhibit free Factor Xa, clot-bound Factor Xa and Factor Xa bound to the prothrombinase complex. Rivaroxaban is approved in the US and elsewhere for stroke prevention for atrial fibrillation and for the prevention of VTE in adult patients after elective hip or knee replacement surgery, based on large clinical trials where rivaroxaban was compared to warfarin or enoxaparin respectively, while apixiban is being reviewed.24,27

**Perioperative Management of the New Oral Anticoagulants**

In the US, warfarin is still a problem for clinicians because the balanced prothrombin complex concentrates (PCCs) that contain all four factors (II, VII, IX, X) like Beriplex and Octaplex for immediate INR reversal are not available.25 Vitamin K takes days to work, ~4 units of fresh frozen plasma (FFP) is required with transfusion risk issues and volume overload, and FFP never restores the INR to baseline but usually to ~1.4-1.6 which is the baseline INR for FFP.28

The French Study Group on thrombosis and hemostasis have proposed perioperative management strategies.29 They suggest for procedures with low hemorrhagic risk, a therapeutic window of 48 hours (last administration 24 hours before surgery, restart 24 hours after) is proposed. For procedures with medium or high hemorrhagic risk, they suggest stopping therapy 5 days before surgery to ensure complete elimination in all patients. Treatment should be resumed only when the risk of bleeding has been controlled. In patients at high thrombotic risk (e.g. those in atrial fibrillation with a history of stroke), bridging with heparin is proposed. They suggest prohemostatic agents should not be given for prophylactic reversal due to their uncertain benefit-risk.29

**Monitoring the New Oral Anticoagulants**

Although routine monitoring of the new anticoagulants is not standard, if needed they can be evaluated with specialized tests. For dabigatran, thrombin clotting time (TT), ecarin clotting time (ECT), and activated partial thromboplastin time (aPTT) can measure its effects.30 The aPTT provides a qualitative assessment of anticoagulation. Although there is no specific antidote to antagonize the anticoagulant effect of dabigatran, because of its short duration of effect drug discontinuation should be considered as previously noted. With overdose,
dabigatran can also be dialyzed in patients with renal impairment. In instances of life-threatening bleeding, prohemostatic agents such as PCCs can be considered. For rivaroxaban prolongation of most standard hemostatic tests are too variable and specialized tests evaluating antiXa are required. Recent data also suggests PCCs completely reverses the anticoagulant effect of rivaroxaban in healthy subjects but only partially reverses dabigatran at the PCC doses of 50 IU/kg used in the study. Dabigatran can also be dialyzed.

In summary, for those who require urgent surgery, managing patients who receive dabigatran, rivaroxaban and other novel oral anticoagulants require cessation of the drug. However, risk versus benefit considerations need to be considered. It is important to note the therapies for reversal are off label uses from the literature as referenced, but provide important perspective for perioperative management for the clinician faced with managing patients receiving these agents.

USE OF NEW ANTICOAGULANTS FOR NEURAXIAL ANESTHESIA

When used with neuraxial anesthesia, an epidural catheter should not be removed earlier than 18 hours after the last administration of rivaroxaban, and the next rivaroxaban dose should be administered no earlier than 6 hours after the removal of the catheter and as noted in the package insert (http://www.xareltohcp.com/sites/default/files/pdf/xarelto_0.pdf#zoom=100). Recommendations for dabigatran suggest the risk of spinal or epidural hematoma may be increased in cases of traumatic or repeated puncture and by the prolonged use of epidural catheters. After removal of a catheter, an interval of at least 2 hours should elapse before the administration of the first dose of dabigatran etexilate. These patients require frequent observation for neurological signs and symptoms of spinal or epidural hematoma. (http://www.cem.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000829/WC500041059.pdf)

PLATELET INHIBITORS

In patients with myocardial ischemia and/or atherosclerotic vascular disease, inhibiting platelet activation is critical in managing these patients. Platelet inhibitors/antiplatelet agents should also be considered as anticoagulants, and also pose increased risks for bleeding. The antiplatelet agents differ in their modes of action, potency, onsets of action, and indications. Aspirin irreversibly inhibits platelet cyclooxygenase and thromboxane A2, a platelet activator. Aspirin is a relatively weak antiplatelet agent. Nonsteroidal anti-inflammatory drugs also reversibly inhibit cyclooxygenase. Aspirin, however, irreversibly alters the cyclooxygenase so that platelet pool is destroyed until effective replacement occurs from the bone marrow, however resistance can occur. More potent antiplatelet agents include clopidogrel (Plavix) and IIb/IIIa receptor antagonists (abciximab, tirofiban, eptifibatide). Clopidogrel, prasugrel, and ticagrelor are more potent than aspirin, and inhibit platelets by selectively and irreversibly binding to the P2Y12 receptor to inhibit the adenosine diphosphate–dependent pathway of glycoprotein IIb/IIIa–receptor activation although resistance can occur. Clopidogrel is the major agent used with the least knowledge available about how to manage these patients or monitor its effects.

Antiplatelet therapy with aspirin and clopidogrel is standard care following revascularization by percutaneous coronary intervention with stent insertion. This so-called dual therapy is recommended for up to 4 weeks after intervention for bare-metal stents and for 6-12 months after intervention for drug-eluting stents. Vincenzi noted a 45% complication rate and a mortality of 20% reported in patients undergoing noncardiac surgery after coronary artery stenting. Discontinuation of antiplatelet drugs appeared to be of major influence on outcome. They prospectively evaluated 103 patients receiving stents within 1 year before noncardiac surgery. Antiplatelet drug therapy was not, or only briefly, interrupted. Heparin was administered to all patients. Of 103 patients, 44.7% developed complications after surgery; 4.9% of the patients died. All but two (bleeding only) adverse events were of cardiac nature. Most complications occurred early after surgery. The risk of suffering an event was 2.11-fold greater in patients with recent stents (<35 days before surgery) compared with percutaneous cardiac intervention more than 90 days before surgery. The clopidogrel package insert suggests if a patient is to undergo elective surgery and an antiplatelet effect is not desired, it should be stopped 5 days before surgery. However, if patients bleed, therapy or monitoring its effects has not been established. Further, the risk compared to the benefit of stopping clopidogrel, need to be weighted against the risk of stent thrombosis, and the need for surgical intervention as well.

Prasugrel has an advantage of increased potency and potentially a lower rate of “resistance”, one of the potential problems for clopidogrel.

PERIOPERATIVE MANAGEMENT OF ANTITHROMBOTIC THERAPY BASED ON GUIDELINES

Recent guidelines from the American College of Chest Physicians in 2012 have been reported. In patients requiring vitamin K antagonist (VKA) interruption before surgery, they recommend stopping VKAs 5 days before surgery instead of a shorter time before surgery (Grade 1B). In patients with a mechanical heart valve, atrial fibrillation, or VTE at high risk for thromboembolism, they suggest bridging anticoagulation instead of no bridging during VKA interruption (Grade 2C); in patients at low risk, they suggest no bridging instead of bridging (Grade 2C). In patients who require a dental procedure, they suggest continuing VKAs with an oral prohemostatic agent or stopping VKAs 2 to 3 days before the procedure instead of alternative strategies (Grade 2C).
In moderate- to high-risk patients who are receiving acetylsalicylic acid (ASA) and require noncardiac surgery, they suggest continuing ASA around the time of surgery instead of stopping ASA 7 to 10 days before surgery (Grade 2C). In patients with a coronary stent who require surgery, they recommend deferring surgery > 6 weeks after bare-metal stent placement and > 6 months after drug-eluting stent placement instead of undertaking surgery within these time periods (Grade 1C); in patients requiring surgery within 6 weeks of bare-metal stent placement or within 6 months of drug-eluting stent placement, they suggest continuing antiplatelet therapy perioperatively instead of stopping therapy 7 to 10 days before surgery (Grade 2C).

**PROCOAGULANT AGENTS**

Anesthesiologists are often called on to correct coagulopathy in patients who are actively bleeding despite transfusion and other therapies. Further, many patients may also have received any one or combination of the anticoagulant agents just reviewed. Therefore, clinicians must understand some of the potential procoagulant therapies available to reverse bleeding or anticoagulation therapy. These agents include antifibrinolytics, protamine, desmopressin, fibrinogen, purified protein concentrates, recombinant factor VIIa (rFVIIa), and topical hemostatic agents, and each will be considered separately.

**ANTIFIBRINOLYTIC AGENTS**

Antifibrinolytic agents include Epsilon-Aminocaproic Acid (EACA) and Tranexamic Acid (TXA), and aprotinin. EACA and TXA are lysine analogs that competitively inhibit activation of plasminogen to reduce conversion of plasminogen to plasmin, an enzyme that degrades fibrin clots, fibrinogen, and other plasma proteins, including the procoagulant factors V and VIII. TXA also directly inhibits plasmin, but higher doses are required than are needed to reduce plasmin formation. The lysine analogs have variable effects on reducing bleeding, especially EACA, and published safety data on these agents are limited. Most of the efficacy data for these agents are reported with TXA, and represent small studies or from meta-analyses of pooled previously published data. Antifibrinolytic agents have also been reported for blood conservation in orthopedic and other surgical procedures.

One important TXA study is the CRASH2 study that evaluated safety and efficacy of TXA in 20,211 adult trauma patients randomized to 1 g load and infusion over 8 h to placebo. The primary outcome was death in hospital within 4 weeks of injury, and was described with the following categories: bleeding, vascular occlusion (myocardial infarction, stroke and pulmonary embolism), multiorgan failure, head injury, and other. All-cause mortality was significantly reduced with tranexamic acid (1463 [14.5%] tranexamic acid group vs 1613 [16.0%] placebo group; p=0.0035). The risk of death due to bleeding was significantly reduced (489 [4.9%] vs 574 [5.7%]; p=0.0077). TXA is also approved in the US for cyclic heavy menstrual bleeding at a dose of 3.9 g/day (Lysteda).

Aprotinin is a broad spectrum protease inhibitor and antifibrinolytic agent, originally approved for reducing bleeding in coronary surgery in the US, but removed from marketing in 2008 based on the BART study. However, recent reviews by the Canadian and European Union have concluded that aprotinin’s benefits in preventing blood loss outweigh its risks in patients undergoing isolated heart bypass surgery who are at high risk of major blood loss. Aprotinin was suspended following the preliminary results of the BART study, a randomized controlled trial in high-risk heart surgery patients. These results appeared to show an increased death rate in patients receiving aprotinin after 30 days compared to patients taking other medicines, and led to the early discontinuation of the study by its data safety monitoring board. Based on the final results of the BART study as well as the results of other clinical studies, data from the scientific literature, reports of side effects and information submitted by the companies that market antifibrinolytic medicines, the Committee found there were a number of problems with the way the BART study was conducted, which cast doubt on the previous conclusions. These included the imbalances in the way blood-thinning medicines such as heparin were used, inappropriate monitoring of the use of these medicines and how problems with the way that data from some patients were excluded from the initial analysis. The Committee found that the BART study’s results were not replicated in other studies and that the overall data available showed that aprotinin’s benefits is greater than its risks in the restricted indication.

**DESMOPRESSIN**

Desmopressin (DDAVP) is the V2 analog of arginine vasopressin that stimulates the release of ultralarge von Willebrand factor (vWF) multimers from endothelial cells. VWF mediates platelet adherence to vascular subendothelium by functioning as a protein bridge between glycoprotein Ib receptors on platelets and subendothelial vascular basement membrane proteins. DDAVP shortens the bleeding time of patients with mild forms of hemophilia A or von Willebrand disease. Surgical patients who might benefit from use of DDAVP are not clear. DDAVP is administered intravenously at a dose of 0.3 mg/kg, and should be given over 15-30 minutes to avoid hypotension. Most studies have not confirmed the early reported efficacy during complex cardiac surgery. Mannucci noted there have been 18 trials of desmopressin in 1295 patients undergoing cardiac surgery that show a small effect on perioperative blood loss (median decrease, 115 ml).
RECOMBINANT COAGULATION PRODUCTS

Recombinant coagulation products are used to manage bleeding in patients with hemophilia, von Willebrand’s disease (vWD), or acquired inhibitors to antihemophilic factor (e.g., AHF concentrates, factor IX concentrates, factor VIIa concentrate, factor IX complexes, anti-inhibitor coagulant complexes). Recombinant activated factor VIIa (rFVIIa; NovoSeven, Novo Nordisk) is approved for hemophilia patients with inhibitors to treat bleeding. Currently, rFVIIa is used off label as a prohemostatic agent in complex clinical situations for life threatening hemorrhage.

Recombinant factor VIIa produces a prohemostatic effect by forming a complex with tissue factor (TF) that is expressed at the site of injury, and locally initiates hemostatic activation. TF is a membrane-bound glycoprotein that is expressed on subendothelial cells after tissue injury and loss of endothelial protective mechanisms. Circulating FVIIa accounts for nearly 1% of circulating FVII, and is inactive until bound with TF9. When rFVIIa is administered, it binds to TF that activates factor X to factor Xa, leading to the generation of thrombin (FIIa) and resulting fibrin formation and platelet activation. Giving rFVIIa to patients with multiple hemostatic abnormalities may result in added thrombin generation both on the surface of activated platelets but also at the local site of injury. Multiple publications report rFVIIa in surgical patients and cardiac surgical patients including a recent reported analysis of the clinical studies. Other publications have reported the cessation of bleeding following major trauma with refractory hemorrhage and coagulopathy. The therapeutic dose of rFVIIa in non hemophilia patients are not established. Guidelines as reported by Goodnough and Despotis for off label use in patients with life threatening hemorrhages.

We evaluated the rate of thromboembolic events in all published randomized, placebo-controlled trials of rFVIIa used on an off-label basis from 35 randomized clinical trials (26 studies involving patients and 9 studies involving healthy volunteers) to determine the frequency of thromboembolic events. Among 4468 subjects, 498 had thromboembolic events (11.1%). Rates of arterial thromboembolic events among all 4468 subjects were higher among those who received rFVIIa than among those who received placebo (5.5% vs. 3.2%, P=0.003). Rates of venous thromboembolic events were similar among subjects who received rFVIIa and those who received placebo (5.3% vs. 5.7%). Among subjects who received rFVIIa, 2.9% had coronary arterial thromboembolic events, as compared with 1.1% of those who received placebo (P=0.002). Rates of arterial thromboembolic events were higher among subjects who received rFVIIa than among subjects who received placebo, particularly among those who were 65 years of age or older (9.0% vs. 3.8%, P=0.003); the rates were especially high among subjects 75 years of age or older (10.8% vs. 4.1%, P=0.02). Overall, in a large and comprehensive cohort of persons in placebo-controlled trials of rFVIIa, treatment with high doses of rFVIIa on an off-label basis significantly increased the risk of arterial but not venous thromboembolic events, especially among the elderly. Other major issues regarding rFVIIa include costs and dosing.

REVERSAL OF VITAMIN K ANTAGONISTS
ASSOCIATED COAGULOPATHY

Prohemostatic agents are often needed to urgently reverse the anticoagulant effect of warfarin in the perioperative setting. Treatments available for reversal include vitamin K, fresh frozen plasma (FFP), prothrombin complex concentrates (PCCs), and rFVIIa. Warfarin reversal is becoming a major indication for FFP in some hospitals. PCCs were originally developed for repleting factor IX in hemophilia B, and contain standardized amount of FIX along with various amounts of other vitamin K dependent factors (prothrombin, FVII, FX, protein C and S). PCCs are recommended in guidelines as primary treatment for reversal in patients with life-threatening bleeding and an elevated international normalized ratio (INR), and rFVIIa may be considered as an alternative. Compared with FFP, evidence suggests PCCs offer quicker INR correction and improved bleeding control; they also have a lower infusion volume and are more readily available without cross matching. Although there are historical concerns regarding potential thrombotic risk with PCCs, present-day PCCs are much improved.

FIBRINOGEN

Fibrinogen is an under recognized coagulation factor critical for producing effective clot in surgical patients, and data supports it as a predictor of perioperative bleeding. During the third trimester of pregnancy, fibrinogen levels are elevated to >400 mg/dL. Bleeding increases for each 100 mg/dL decrease in fibrinogen level in parturients. These clinical data highlight critical roles of fibrinogen in the prevention of excessive bleeding, thus adequate plasma levels (~ 200 mg/dL) need to be considered when treating life threatening bleeding. Fibrinogen can be replete by human plasma-derived fibrinogen concentrate; otherwise, fibrinogen-rich cryoprecipitate can be given (one unit per 10-kg increases fibrinogen by 50–70 mg/dL). In Europe, fibrinogen concentrates are available and cryoprecipitate is not used. A fibrinogen concentrate (RiaSTAP, CSL Behring) has just been granted licensing as an orphan drug for treating bleeding in patients with congenital afibrinogenemia or hypofibrinogenemia, but not for patients with dysfibrinogenemia. Data to support the approval came from a study of 15 patients with afibrinogenemia who received 70 mg/kg of fibrinogen concentrate and achieved a target level of fibrinogen expected to prevent bleeding.

TOPICAL HEMOSTATIC AGENTS

Topical hemostatic agents are used extensively by orthopedic, neuro, cardiac, and vascular surgeons to promote hemostasis locally at the site of surgery.
and vascular. These agents can be classified based on their mechanism of action and include physical or mechanical agents, caustic agents, biologic physical agents, and physiologic agents. One of the widely used agents is topical thrombin.\(^{71}\) Bovine-derived thrombin until recently was the only topical thrombin available, and has the potential to induce immune responses following human exposure.\(^{71}\) There are now purified human thrombin (purified from multiple donors) and a recombinant thrombin for RECOTHROM.\(^{TM}\)

**THE FUTURE**

The potential for bleeding in a perioperative setting represents a growing problem for clinicians. The increasing use of anticoagulation agents creates a need for multiple pharmacologic approaches. The growing use of clopidogrel, the new agent prasugrel, and newer anticoagulants will continue to pose new paradigms and potential problems in managing surgical patients. Newer therapies including recombinant therapies provide clinicians with the ability to give key coagulation proteins to treat hemorrhage when standard therapies are ineffective.

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LEARNER OBJECTIVES

- Update on the physiology and current application of veno-venous and veno-arterial ECMO in acute respiratory failure and circulatory shock
- Update on current applications of ventricular assist devices and the total artificial heart as bridge to recovery, transplantation or destination therapy
- Update on the expanding role of bedside ultrasound and echocardiography in the ICU and its practice by intensivists
- Update on the promise and limitations of biomarkers in the early diagnosis of acute kidney injury.

EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO)

Introduction

ECMO implies extra-corporeal membrane oxygenation, but in practice the two types of ECMO fulfill quite different objectives.

Veno-venous (VV) ECMO provides respiratory support by placing an ancillary “lung” proximal to the native lungs, thereby facilitating pre-oxygenation and extracorporeal carbon dioxide removal (ECCO2R) from the venous blood so that the native lungs can be rested.\(^3\)

Veno-arterial (VA) ECMO is analogous to cardiopulmonary bypass (CPB), in which the function of the heart is replaced or supplemented by the ECMO pump, with our without lung replacement.

The most important advance in ECMO in recent years has been progressive miniaturization. Central to this is the development of a poly-methylpentene (PMP) membrane oxygenator (Quadrox D) that is very small and portable, driven by a centrifugal pump.\(^2\) This system avoids the plasma leakage associated with conventional standard hollow-fiber oxygenators. This in turn decreases the risk of thrombogenesis, thrombocytopenia, disseminated intravascular coagulation (DIC), bleeding and blood and blood product transfusion.

Veno-Venous ECMO (VV-ECMO)

Today a mainstay for pulmonary support in severe acute respiratory failure is VV-ECMO, which creates an oxygenating and ECCO\(_2\)R circuit in parallel to the venous system. It provides no circulatory support, so the patient must be relatively hemodynamically stable.

Traditionally an internal jugular cannula is placed from which venous blood is pumped through the membrane oxygenator and thence returned via cannula placed in the femoral vein and advanced as close to the right atrium (RA) as possible. A recent advance is the development of a single cannula system using a double-lumen bicalve internal jugular cannula (Avalon\(^*\) cannula). There are two inflow ports positioned opposite the superior vena cava (SVC) and inferior vena cava (IVC) ostia in the RA; a central outflow port directs oxygenated blood into the RA toward the tricuspid valve. Not only does this cannula decrease the risk of recirculation inherent in the two catheter system, but it facilitates mobilization of patients during VV-ECMO.\(^3\)

Miniaturization of the system, especially with the advent of the Quadra D oxygenator, has progressed to the extent that the entire VV-ECMO circuit can be mounted on an intravenous (IV) pole. Teams from a tertiary care center can go to regional centers to institute VV-ECMO and safely transport patients back to the institution for ongoing care or possibly lung transplantation.\(^4\) Patients on VV-ECMO can be extubated and extensively mobilized and ambulated.

Indications for VV-ECMO

1. Rescue Therapy in ARDS.

   Initial studies, such as the U.S. ECMO trial (1974–1977), used ECMO with complete lung collapse, and dismal survival (9%). Over the next 10 years,Gattinoni and his colleagues in Milan, Italy demonstrated the effectiveness of maintenance of low frequency positive pressure ventilation (LFPPV, rate 3–5/min), utilizing low flow VV-ECMO for CO2 removal (ECCO\(_2\)R).\(^5\) This approach was associated with a 49% survival in very severe ARDS; in survivors, lung function improved within 48 hours. In a subsequent randomized study in the U.S., Morris et al. compared LFPPV-ECCO2R with PC-IRV, using computerized protocols in 40 patients.\(^6\) There was no statistical significance in 30-day survival (33% vs 42%).

   The most recent large scale RCT is the CESAR trial (Conventional Ventilatory Support versus ECMO for Severe Adult Respiratory Failure) performed on 180 adults in the UK.\(^7\) An independent central randomization service randomly assigned patients to either treatment modality within seven days of the onset of severe ARDS (Murray score > 3.0, pH < 7.20). Patients who were referred to a specialty center for consideration of ECMO had significantly improved 6-month survival (63% vs. 47%). However, 20% of the referred patients did not undergo ECMO and had an 80% survival, thus some of the benefit was likely due to the provision of protective lung ventilation in a highly specialized center. Despite these mixed results, interest in VV-ECMO in ARDS continues, particularly in facilitating “lung rest” – i.e. minimizing ventilator induced lung injury (VILI) by avoidance of the adverse effects of high airway pressures and alveolar overdistension as well as...
circulatory resuscitation, stabilization and assessment in the ICU, and avoids the need for cardiotomy. It allows peripheral cannulation to be rapidly accomplished, even in cardiogenic shock, as “bridge to a decision”. Perioperative care is provided via a veno-arterial circuit (VA-ECMO). VA-ECMO is primarily indicated as rescue therapy for cardiogenic shock in the operating room and cardiac catheterization laboratory. It is relatively rapidly and easily applied, but we must be careful to restrict it to potentially reversible conditions; otherwise we may find ourselves in the situation where “no-one dies without VA-ECMO”.

2. Bridge to Lung Transplantation.

Candidates for lung transplantation who develop an acute decompensation requiring tracheal intubation and mechanical ventilation are at very high risk for ventilator associated pneumonia (VAP) and ventilator induced lung injury (VILI). This may result in the patient losing the opportunity for transplantation. Institution of VV-ECMO may actually allow tracheal extubation, thus avoiding VAP and VILI, and also facilitating mobilization and enhanced conditioning prior to lung transplantation. Preoperative ECMO does not appear to adversely affect mid-term survival. After surgery, we have used VV-ECMO for rescue therapy for ischemic-perfusion injury or acute rejection.

Veno-Arterial ECMO (VA-ECMO)

If oxygenation is not sufficiently supported by VV-ECMO, or the patient is hemodynamically unstable, ECMO is provided via a veno-arterial circuit (VA-ECMO). This provides partial or near complete circulatory assist (analogous to CPB) and more complete oxygenation of arterial blood. However it requires cannulation of a major artery (most often, the femoral artery) with increased risk of vascular injury, embolism, and limb ischemia. Placement of a distal reperfusion catheter adjacent to the arterial cannula or in the posterior popliteal artery can preserve distal limb perfusion.

Unlike VV-ECMO, VA-ECMO remains an expensive, complex, resource intensive modality that requires considerable expertise. It requires full systemic anticoagulation to prevent contact activation-induced thrombosis, and there is high risk of major bleeding and coagulopathy, thromboembolism, stroke, sepsis, and multisystem failure. An experienced perfusionist needs to be at the bedside or at the very least in house on 24-hour call for emergencies, with frequent bedside checks.

VA-ECMO is primarily indicated as rescue therapy in cardiogenic shock, as “bridge to a decision”. Peripheral cannulation is rapidly accomplished, even in the ICU, and avoids the need for cardiotomy. It allows circulatory resuscitation, stabilization and assessment of neurologic status, as well as evaluation of myocardial recovery or candidacy for insertion of a ventricular assist device (VAD). There is increasing application of VA-ECMO as rescue therapy for cardiogenic shock in the operating room and cardiac catheterization laboratory. It is relatively rapidly and easily applied, but we must be careful to restrict it to potentially reversible conditions; otherwise we may find ourselves in the situation where “no-one dies without VA-ECMO”.

VENTRICULAR ASSIST DEVICES AND THE TOTAL ARTIFICIAL HEART

Ventricular Assist Devices

Indications

There has been considerable progress in the utilization and effectiveness of the ventricular assist device (VAD) as a means of support for the patient with end-stage heart disease (ESHD) (Table 1). The VAD may be placed (1) as a bridge to decision, i.e. as a temporizing, life-saving intervention during a crisis to provide support until a decision can be made regarding further definitive therapy; (2) as a bridge to a bridge, i.e. as a short-term rescue device that is emergently placed to provide support until a longer-term, larger device can be placed; (3) as a bridge to recovery, i.e. to provide life-saving support during an acute crisis, until the ventricle recovers and the patient can be weaned off the VAD; (4) as a bridge to transplant, considering that at least 50% of patients awaiting heart transplant would die because of inability to obtain a timely organ; and (5) as destination therapy, in patients with ESHD who are not candidates for heart transplantation.

The VAD may be placed to support the left ventricle (LV), i.e. an LVAD, right ventricle (RV), i.e. an RVAD, or both ventricles (BiVAD). However, all internal long-term devices are currently available as an LVAD only.

Anatomic and Physiologic Considerations

Correction of Structural Abnormalities

 Certain structural abnormalities must be corrected at the time of VAD implantation to avoid abnormal intracardiac circuits. Tricuspid regurgitation should be repaired to enhance RV function, which is especially important in a patient receiving an LVAD only. Aortic regurgitation must be corrected to prevent blood pumped from the outflow limb of the LVAD in the ascending aorta to recirculate back into the LV. Mitral stenosis must be corrected to facilitate ventricular (and VAD) filling from the left atrium. Patent foramen ovale, atrial and ventricular septal defects must be closed to avoid the development of a left to right shunt when the left atrium and LV are decompressed by the LVAD and become low pressure chambers.

Pulmonary Vascular Resistance

It is essential to control elevated pulmonary vascular resistance (PVR) in patients receiving a VAD. With an LVAD, an elevated PVR will compromise delivery of blood from the right to the left side of the heart, diminish LVAD filling and decrease LVAD
output. It may also contribute to right heart failure in the unassisted right ventricle. With an RVAD, elevated PVR may result in excessive right sided atrial pressure. An update on the management of elevated PVR is provided in the next section of this Review Course.

Management of RV Function

Maintenance of effective RV function is essential to ensuring good outcome after LVAD placement. Acute right heart failure (RHF) may occur in up to 40% of patients receiving an LVAD. It is associated with an increased rate of reoperation for bleeding, postoperative acute kidney injury (AKI), ICU length of stay (LOS) and early mortality. Successful bridge to transplantation is impaired and about a third of the patients with RHF ultimately require an RVAD.

The principles of the management of right ventricular function include (1) maintenance of RV coronary perfusion pressure by keeping mean arterial pressure (MAP) > 80 mmHg using vasopressor drugs; (2) avoidance of RV overload by keeping central venous pressure (CVP) as close to 10 mmHg as possible; (3) control of elevated PVR and avoidance of excessive afterload by use of appropriate pulmonary vasodilator therapy; (4) enhancement of RV contractility by administration of inodilator drugs (see below).

A fifth principle specific to newer LVADs is the avoidance of excessive LV emptying. Second and third generation LVADs provide non-pulsatile flow and maintain a parallel circuit of flow out of the native aorta. Excessive pump rates may cause the LV to empty, which induces leftward septal shift and RV dyskinesis. This may be revealed on transesophageal echocardiography (TEE) by conversion of the short-axis round LV to a “D”-shape induced by the flattened or convex intraventricular septum.

Inodilator Therapy

Inodilator therapy is usually provided by the phosphodiesterase (PDE) III inhibitor, milrinone, with or without superadded dobutamine, a direct acting beta-1 and beta-2 agonist. These agents both increase cyclic adenosine monophosphate (cAMP), the former by decreasing its breakdown and the latter by increasing its production. Milrinone’s vasodilator effects may be limiting and invariably require concomitant vasopressors administration; dobutamine preserves blood pressure but its chronotropic and bathmotropic effects promote arrhythmias. Combining a PDE inhibitor with a beta-adrenergic agonist provides superior enhancement of RV stroke volume than either drug used alone, and allows much lower dosage of each drug, with fewer side effects.

Levosimendan, a potent inodilator not currently available in the USA, acts independently of the beta receptor or cAMP by stabilization of the troponin C-calcium complex in myofibrils, strengthening the actin-myosin cross bond. Levosimendan may have a more sustained benefit on postoperative stroke volume than milrinone and require less norepinephrine (NE) vasoconstrictor support. In patients with low EF, the combination of levosimendan with dobutamine is more effective in improving stroke volume than the combination of milrinone and dobutamine. Levosimendan undergoes biotransformation to an active metabolite that exerts potent effects for up to a week, so it is not infused for more than 24 hrs, and there may be a benefit to starting the infusion 48 hrs before surgery.

First Generation VADs: Pulsatile Flow

Thoratec HeartMate XVE

The Thoratec HeartMate I or XVE became established as the LVAD that achieved the widest use in the decade from its introduction in 1994 through about 2005. It served primarily as a bridge to transplant, but in 2001 was shown to be superior to maximal medical therapy in survival as well as quality of life in destination therapy. It has a large metallic pump placed sub-diaphragmatically but pre-peritoneally in the abdomen (LVAD pocket), with an inflow from the left ventricle (LV) and an outflow into the ascending aorta above the aortic valve. Porcine valves are placed in the inflow and outflow tubes just proximal and distal to the pump. The pump has a driveline that provides electrical power and emerges from the abdominal wall some distance from the LVAD pocket. The interior of the pump consists of a rotating flange that moves up (systole) and down (diastole) a circular cam, generating pulsatile flow out the aorta and essentially emptying the LV during each cycle.

The HeartMate XVE has a number of design benefits. It maintains pulsatile flow so the patient has a palpable pulse and blood pressure can be measured externally by a blood pressure cuff. Its physiology most closely mimics normal hemodynamics, i.e. the LV fills and empties and thereby supports right ventricular (RV) function. The entire LV stroke volume is ejected into the aorta above the valve so that aortic stenosis becomes redundant (and the valve may actually be sewn closed). The interior of the pump is lined with textured polyurethane that becomes endothelialized within a few days. This so greatly reduces contact activation of procoagulants that the risk of thrombosis is minimized and patients do not need to be fully anticoagulated with Coumadin – aspirin is sufficient – which in turn greatly decreases the risk of bleeding.

However, the HeartMate XVE has numerous limitations that have rendered it virtually obsolete today. It is extremely loud, which may disrupt sleep for the patient and their spouse. Its large size precludes placement in children or small adults. Even in larger adults, its anatomic position may compress the stomach to the extent of causing a gastric outlet syndrome and making placement of an enteral feeding tube very difficult. The new endothelial lining expresses abnormal antigens that increase the risk of antibody formation and rejection with a subsequent heart transplant. Systemic hypertension increases pressure fatigue to the LVAD and its components and shortens its expected life, which at best is no more than two years.
The PVAD and IVAD

The Thoratec Company also produced a first generation, pulsatile external device called the PVAD (paracorporeal VAD), which consists of a fist-sized pump that lays on the patient’s abdomen. It has the advantage of being able to provide LVAD, RVAD and BiVAD support so that it could be utilized as an in-hospital bridge to transplant or in conjunction with an internal LVAD to provide short or longer term RV support. However, the cannulas are large and the console is huge. More recently, the company has modified the pumps to allow them to be placed subcutaneously (IVAD, intracorporeal VAD) and developed a much small, portable console, that allows the device to be used as a bridge to transplant or destination therapy out of hospital.

Second Generation VADs: Non-Pulsatile Axial (Rotary) Flow

Thoratec HeartMate® II

The Thoratec HeartMate® II is a pencil-like pump that rotates at 8000-10000 rpm and creates axial flow within a long term internal LVAD that has a number of advantages over its predecessor. It has virtually replaced the HeartMate® XVE as a bridge to transplant or destination therapy. The profile of the HeartMate® II is less than a quarter than that of the HeartMate® XVE, creating a much smaller LVAD pocket with no gastric compression, and allowing placement in small adults. It is much quieter, has far fewer moving parts, and much greater longevity. Compared to the HeartMate® XVE, the HeartMate® II provides significantly greater two year survival (58% vs. 24%) and freedom from disabling stroke or device malfunction (46% vs. 11%).

The challenge of the HeartMate® II is that its physiology is far more complex and its hemodynamic management requires considerably more attention to detail. It provides non-pulsatile flow so the patient has no palpable pulse, which precludes cuff blood pressure measurement and requires Doppler assessment.

Because drainage from the LV is continuous, excessive flow generated by high rpm in the LVAD may cause the LV chamber to collapse, especially if the inflow cannula is sucked against the LV wall (a “suction event”). This in turn displaces the intraventricular septum and may acutely compromise RV function. A similar situation may be caused by intravascular hypovolemia. The relative volume (or unloading) status of the LV is indicated on the LVAD monitor by a unitless parameter called the pulsatility index (PI), which must be closely assessed and kept between 4.0 and 6.0.

Pump flow is calculated based on power and blood viscosity; at the extremes of flow it is subject to error and may indicate “normal” flow in low flow states such as cardiac tamponade 12. The nature of the device precludes polyurethane coating, so patients must be fully anticoagulated, which increases the risk of postoperative bleeding. However, thromboembolic cerebrovascular events appear to be if anything less common than with the HeartMate XVE (see above).

Abiomed® Impella® 5.0

The Abiomed® Impella® device is a short term, external device used as a bridge to decision or bridge to a bridge. It consists of a long cannula that is placed via the femoral or axillary artery through to the ascending aorta and across the aortic valve into the LV. There the rapid rotational force of the microaxial rotary pump at its tip generates forward flow up to 5 L/min. It is designed for short-term (< 24 hrs) use only. It cannot be placed in the presence of aortic stenosis, and prolonged use damages red blood cells and may induce a hemolytic anemia.

Third Generation VADs: Non-Pulsatile Centrifugal Flow

There is an emerging series of third-generational long term centrifugal LVADs, all of which are still investigational in the U.S. A major advance is that through magnetic or hydrodynamic levitation there is no contact between the impeller and the drive mechanism. There is almost minimal contact with the blood, and the impeller rotates centrifugally much more slowly than the rotary devices, at 2750-3000 rpm. The advantages claimed are decreased hemolysis and thrombogenesis, and greater mechanical durability.

Levitronix® CentriMag

The Levitonix® CentriMag device is an external, short-term device that may be utilized as an LVAD, RVAD or BiVAD. The magnetically levitated centrifugal pumps are small and may be attached to an IV pole; the cannulas are very small (7 mm), so the device can be placed quickly and easily in the OR or Cath Lab. A console provides rpm and flow rates determined by ultrasound. Since its introduction at our medical center in 2007, the CentriMag has become the predominant VAD utilized as a bridge to decision, bridge to a bridge or even short-term bridge to transplant.

The CentriMag has a further advantage in that, because its cannulas are all external, hypovolemia may be detected by a phenomenon known as “chattering”, when the cannulas start to vibrate.

The LVAD is FDA-approved for 6 hr only, and the RVAD for 30 days, but in our practice the devices have been left in place for considerably longer. Although the external nature of the device mandates constant supervision, with care, it is possible to allow patients to get out of bed, mobilize and even ambulate, but in most cases, the device is converted to a longer-term device before the patient leaves the ICU.

Terumo® DuraHeart™

The Terumo® DuraHeart™ is a third-generation long-term LVAD in which the pump is provided by a magnetically levitated impeller with centrifugal flow. In other respects its concept is similar to the HeartMate® II, with a small intra-abdominal, preperitoneal LVAD pocket, driveline and external battery packs. The device is approved in the European Union (EU), where compared to pulsatile LVADs it demonstrates significantly improved survival (85% at 6 months, 79%
Serum Creatinine

Serum creatinine (SCr) is not a marker of renal injury, but of renal function, and reflects the balance between muscle creatinine production and renal excretion. SCr is a useful marker of glomerular filtration rate (GFR) in a steady state, but it is important to appreciate that the relationship between SCr and GFR is inverse and exponential. A doubling of the serum creatinine implies a halving of the GFR. There are numerous limitations to SCr as a reflection of steady state GFR as well as of acute changes in GFR.

Many physiologic molecules (e.g. glucose, protein, ketones) or drugs (e.g. cephalosporins) interfere with the chromogenic assay for creatinine. N-acetylcysteine (NAC), an antioxidant renoprotective agent in radiocontrast nephropathy (RCN) actually decreases SCr levels.

SCr does not increase above the normal range until GFR is <50 mL/min, so any decrease in GFR above this level will still be associated with a “normal” SCr. This is pertinent in the elderly (whose normal GFR is 50-80 mL/min) and cachectic patients (who have very low creatinine generation). Creatinine is freely soluble and distributes throughout the total body water (TBW), so perioperative increases in TBW are reflected by artfactually low SCr immediately after surgery.

Importantly, it may take 2 to 7 days before the SCr reaches a new steady state that reflects acute changes in GFR. This explains why intraoperative AKI is so often reflected by a postoperative SCr that does not peak until 5-7 days after surgery. Indeed, after a transient renal insult (e.g. suprarenal aortic cross-clamping) SCr may increase for a few days while GFR is actually recovering.

Cystatin C

Cystatin C is a cysteine-protease inhibitor that is released into the circulation by all nucleated cells. It is completely filtered by the glomerulus, reabsorbed and not secreted by the tubules; thus, increased serum cystatin C levels reflect decreased GFR, and increased urinary levels reflect tubular injury. Unlike creatinine, cystatin C levels are not affected by muscle mass, age or gender, and there is evidence that it more accurately tracks GFR and responds more quickly. However, certain factors such as cigarette smoking, inflammation and immunosuppressive therapy do independently elevate cystatin C.

Elevation of urinary cystatin C within 6 hr of cardiac surgery has been shown to have a strong correlation with AKI defined by subsequent elevation of SCr, and it has been suggested that preoperative cystatin C is a better predictor of postoperative AKI than SCr. On the other hand, cystatin C has been found to be a poor predictor of AKI and the need for renal replacement therapy (RRT) in the ICU.

Classic Biomarkers of Tubular Injury

Beta-2 Microglobulin

Beta-2 microglobulin (B2M) is a small protein component of the major histocompatibility complex that is present on the surface of almost all cells. It is normally filtered by the glomerulus and then undergoes partial tubular reabsorption. The ratio of serum to urine B2M may help distinguish glomerular from tubular
injury. In the former, serum B2M increases because it is not filtered. In the latter, urinary B2M increases because it is not reabsorbed.

**N-Acetyl Beta D-Glucosaminidase (NAG)**

Increased urinary concentration of the tubular enzyme, N-acetyl beta D-glucosaminidase (NAG) is an index of subclinical tubular injury. Urinary NAG levels, or the ratio of its isoenzymes, is used in the early detection of rejection after renal transplantation. However, the relationship between tubular enzymuria and clinical AKI is not known.

**New Biomarkers of Tubular Injury**

**Neutrophil Gelatinase-Associated Lipocalin (NGAL)**

Neutrophil gelatinase-associated lipocalin (NGAL) is a small 25 kDA polypeptide expressed in proximal tubular cells. Within minutes after ischemic tubular injury NGAL expression is dramatically up-regulated - 3-4 fold within 2-3 hrs, and up to 10,000 fold by 24 hrs. NGAL is readily detected by ELISA in tiny (micromilliter) amounts of urine almost immediately after renal injury, preceding the appearance of NAG and beta2-microglobulin.

Urinary NGAL increases significantly within two hr of CPB in pediatric or adult patients who subsequently go on to develop a 50% increase in postoperative SCr, whose peak is delayed until 2-5 days after surgery. However, the sensitivity and specificity in individual patients is much greater in pediatric (AUC 0.98) than adult cardiac surgery (0.74). This may be explained by pediatric patients having a single insult imposed upon previously normal renal function, whereas, adults have varying preoperative GFR and co-morbidity, with multiple disparate renal insults. Thus although urinary NGAL may represent an early, sensitive, noninvasive urinary biomarker for populations with ischemic and nephrotoxic AKI, it is not yet useful for management decisions in an individual patient.

In fact, NGAL elevation is not specific to AKI because it is an acute phase protein whose production is induced by inflammation and ischemia, and it is a component of the innate immune response to bacterial infection. Elevation of NGAL occurs in many other conditions, including chronic kidney disease, vascular disorders, cancer, preeclampsia, and allergy.

**Interleukin-18 (IL-18)**

Interleukin-18 (IL-18) is a pro-inflammatory cytokine that is involved in ischemic AKI. After CPB, urinary IL-18 is elevated within 4-6 hrs (i.e. later than NGAL), and levels may reflect the severity and duration of ischemic AKI.

**Kidney Injury Molecule-1 (KIM-1)**

Kidney injury molecule-1 (KIM-1) is an immunoglobulin that normally resides in proximal renal tubular cells. After ischemic or nephrotoxic AKI, KIM-1 levels become dramatically elevated, perhaps because the protein plays a role in scavenging apoptotic and necrotic tubular cells. However, compared with NGAL and IL-18, the levels of KIM-1 peak considerably later, at about 12-24 hrs.

A recent review suggests that elevations of KIM-1 are highly predictive of AKI within 24 hr of cardiac surgery, especially ischemic acute tubular necrosis (ATN), but correlate poorly with the need for RRT and mortality.

**Urinary Liver-Type Fatty Acid-Binding Protein (L-FABP)**

Liver-type fatty acid-binding protein (L-FABP) is released from the cytoplasm of proximal tubular cells during ischemic injury, and can be measured in the urine. Unlike NGAL, it is not increased by inflammation and other disease states. A recent study demonstrated that urinary L-FABP was superior to both NAG and NGAL in the early detection of AKI after cardiac surgery.

**Conclusions**

Despite their promise, individual biomarkers of AKI have not yet replaced traditional markers in clinical and investigational studies. There is considerable interest in the development of a panel of early markers of acute tubular injury (NGAL, IL-18, KIM-1, L-FABP) together with a more reliable marker of GFR (cystatin C). The hope is that these panels will be more useful for timing the initial insult and duration of AKI, and in predicting outcome (requirement for dialysis, mortality). Much work remains to be done to validate their sensitivity and specificity in large, diverse patient populations.

**Bedside Ultrasound and Echocardiography in the ICU**

One of the most important developments in critical care in the last decade has been the advent and application of bedside ultrasound and echocardiography in diagnosis and intervention. This has been based upon two concurrent advances. First, increasing miniaturization and portability of ultrasonic and echocardiographic devices that allows bedside (point of care) application. Second, an explosion of interest on the part of intensivists in learning ultrasound and echocardiography and its application into goal-directed management in the intensive care unit (ICU). Instruction, training and potential accreditation and certification are rapidly becoming incorporated into critical care fellowship programs. Bedside ultrasonography and echocardiography do not replace more formal tests, but can be thought of as a technologic extension of the physical examination.

Our emergency room and trauma surgeon colleagues have been years ahead of us in this regard, with the Focused Assessment by Sonography in Trauma (FAST) exam. This is an established approach to search for fluid collections after intra-abdominal trauma in four regions, the sub-xiphoid (pericardial sac); right and left upper quadrants (Morison pouch and splenorenal recess) and the pelvis (pouch of Douglas or rectovesical space).

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A primary challenge of ultrasonography and echocardiography to the intensivist is obtaining an adequate “acoustic window” in the face of interposed lung (during mechanical ventilation) and surgical dressings, tubes, lines etc. The advantages are rapid diagnosis and follow up of cardiopulmonary dysfunction without having to transport the patient to the radiology or cardiology suite. There is evidence that bedside chest ultrasound decreases the need for chest radiographs. Ultrasonography also facilitates safe placement of invasive monitors or drainage catheters.

**BEDSIDE ULTRASONOGRAPHY**

**Vascular Access**

Bedside ultrasonography has rapidly become standard of care for the placement of central lines and arterial cannulation. It facilitates more rapid central line placement with fewer attempts, failures and complications. Transverse and longitudinal views can be obtained that allow real-time visualization of the advent of the needle through the skin and into the correct vessel.

It is also very useful for radial artery cannulation, as well as to access other arterial sites when the radial artery is not usable, notably the axillary artery, but also the ulnar or dorsalis pedis arteries.

**Thoracic Ultrasound**

Bedside ultrasonography is extremely useful for the rapid assessment of pleural effusions, lung consolidation, atelectasis and pneumothorax. It can provides information often missed on the chest radiograph and avoids need for transportation and radiation exposure implicit in computerized tomography (CT) scanning. It can also facilitate safe placement of a pleural catheter to drain pleural effusions.

The lung exam should be performed systematically, dividing the thorax into six regions, upper and lower aspects of the anterior, posterior and lateral chest wall.

There are a number of characteristic signs that help define normal and abnormal lung conditions. Lung sliding, movement of the pleural line between visceral and parietal pleura, provides evidence of pleural movement along the thoracic wall and excludes pneumothorax. A lines are horizontal reverberations that reflect the pleural line in depth and indicate normal lung. Multiple B lines or ultrasound lung comets (ULC) are ring down, vertical reverberations that mask A lines and indicate the presence of an interstitial syndrome such as alveolar pulmonary edema (<3 mm apart) or interstitial lung disease (>7 mm apart). Coalescence of ULCs in severe disease gives the appearance of “white lung”. Severe consolidation (alveolar syndrome) may result in a solid, hyperechoic appearance (hepatization) with or without air bronchograms. Pleural effusions appear as homogeneous, black (hypoechoic) regions during expiration and inspiration surrounding compressed lung.

Diagnosis of pneumothorax is predicated by the absence of lung sliding (i.e. there is gas between the parietal and visceral pleura) and ULCs are not visible. Motionless pleural lines (horizontal A-lines) remain. Absent lung sliding can also be caused by pleural tubes, pleural adhesions and bullous emphysema. To help confirm the diagnosis, the exam should be extended until the pneumothorax pattern (absent lung sliding, horizontal A-lines) is replaced by a normal lung pattern (lung sliding, vertical B-lines), called the lung point.

**BEDSIDE ASSESSMENT OF INTRAVASCULAR VOLUME STATUS**

Subcostal interrogation of the inferior vena cava (IVC) can provide useful information about the patient’s intravascular volume status, and may help guide therapy – for example, fluid administration versus diuresis. A small IVC that decreases in size with inspiration is suggestive of hypovolemia, or a right atrial pressure (RAP) less than 10 mmHg. A full IVC that does not decrease diameter with inspiration is suggestive of an RAP > 10 mmHg.

Bedside assessment of the urinary bladder may be helpful in the differential diagnosis of oliguria or anuria, by ruling out obstructive uropathy.

**BEDSIDE ECHOCARDIOGRAPHY**

**Utilization of Bedside Echocardiography**

Bedside transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE) facilitate rapid assessment of hemodynamic instability caused by a number of etiologies. These include ventricular failure, hypovolemia, pulmonary embolism, acute valvular dysfunction or cardiac tamponade. TTE or TEE are particularly useful in evaluating any of the foregoing conditions after cardiothoracic surgery, and bedside echocardiography may be helpful in the diagnosis of infective endocarditis, aortic dissection, unexplained hypoxemia or intracardiac thrombosis as the source of a peripheral or cerebral embolus.

**Assessment of Left Ventricular Function**

During formal transesophageal echocardiography (TEE), the assessment of left ventricular (LV) ejection fraction (EF) is calculated by accurate assessment of end-diastolic and end-systolic volumes (EDV, ESV), and EF = (EDV-ESV)/EDV. During TTE, the assessment is most often qualitative. Semi-quantitative assessment of global LV function can be obtained by using surrogates such end-diastolic and end-systolic diameter (EDD, ESD) to calculate fractional shortening (FS) = (EDD-ESD)/EDD, or end-diastolic and end-systolic area (EDA, ESA) to calculate fractional area of change (FAC) = (EDA-ESA)/EDA.

Regional wall motion abnormalities (RWMA) can be assessed and are expressed on a scoring system based on whether the segment is normal (1), hypokinetic (2), akinetic (3), dyskinetic (4) or aneurymsmal (5).

**Assessment of Right Ventricular Function**

Acute right heart failure (RHF) is not uncommon in the ICU, especially after cardiac surgery. It may occur with elevated pulmonary vascular resistance (PVR) in
the adult respiratory distress syndrome (ARDS), acute inferior myocardial infarction, pulmonary embolism, fat embolism or after cardiac transplantation. The most important differential is with pericardial tamponade, which may similarly present with elevated RAP. Echocardiographic evaluation of RV function is most commonly based on the ratio of RV to LV EDA. An RVEDA:LVEDA ratio of 0.6 indicates moderate RV dilation, and a ratio of 1 indicates severe RV dilation.\(^{46}\)

**Goal-Directed Hemodynamic Management**

Both TTE and TEE are becoming integrated into goal-directed hemodynamic management in the ICU. There is considerable evidence that they are superior to the bedside pulmonary artery catheter (PAC) in differentiating the etiology of hypotension between cardiogenic (low cardiac output), hypovolemic or distributive (pulmonary embolism). They help determine appropriate hemodynamic therapy, i.e. fluids vs. inotropic agent vs. vasoconstrictor agents. However, to be effective TTE and TEE need to be repeated to assess the response to therapy.

**Specific Conditions Identified by Echocardiography in the ICU**

**Cardiac Tamponade**

Bedside echocardiography is essential to distinguish cardiac tamponade from acute RHF. Characteristic findings induced by the increased pericardial pressure include diastolic collapse of the RV free wall (in early diastole) and RA free wall (in late diastole).

**Dynamic Left Ventricular Outflow Tract Obstruction**

Bedside echocardiography is valuable in the early diagnosis of dynamic left ventricular outflow tract (LVOT) obstruction, which may occur in the absence of asymmetric LV hypertrophy (ASH) or idiopathic hypertrophic subaortic stenosis (IHSS). Dynamic LVOT obstruction is well described in the presence of a small, hypertrophied LV, often found in the elderly patient with chronic hypertension. The patient may develop midventricular obstruction because of hyperdynamic systolic obliteration of the LV cavity, which may be associated with systolic anterior motion (SAM) of the mitral valve that is typically seen in IHSS. It is precipitated by vasodilation, hypovolemia and high endogenous or exogenous catecholamines. LV filling pressures may be elevated, suggesting volume overload, whereas the opposite is the case.

**Takotsubo Cardiomyopathy**

Takotsubo cardiomyopathy (so-named after the Japanese words for octopus pot), apical ballooning syndrome is an acute, potentially fatal but also reversible cause of acute LV failure and cardiogenic shock. It is thought to be induced by massive release of catecholamines (i.e. stress-induced cardiomyopathy). Its presence may be identified at an early stage by bedside echocardiography and lead to more definitive diagnostic measures and therapy.

**Septic Cardiomyopathy**

It is now recognized that myocardial depression may accompany and complicate the response to severe sepsis.\(^{34}\) It may be missed because cardiac output is maintained and filling pressures kept low by the vasodilated, low afterload state. Bedside echocardiography can help diagnosis this at an early stage and help direct appropriate inotropic support.

**Unexplained Hypoxemia**

Unexplained hypoxemia may occur due to reversal of flow across a patent foramen ovale (PFO) when the RAP is elevated by high PVR in pulmonary embolism, ARDS, RHF or severe TR. A microbubble study during TTE or TEE can readily make this diagnosis.

**TRANSTHORACIC VS. TRANSESOPHAGEAL ECHOCARDIOGRAPHY IN THE ICU**

In many situations, TTE provides convenient, repeatable, rapid bedside assessment of cardiac function. There are certain situations where TTE is impracticable, e.g. severe obesity, emphysema, surgical drains and dressings. There are others where the high image quality of TEE is desirable. These include suspected cardiac tamponade, aortic dissection, endocarditis (especially on prosthetic valves) and intracardiac thrombus as a source of cerebral or peripheral embolism. TEE evaluation for cardiac thrombi is mandatory when electrical cardioversion is contemplated for atrial fibrillation that has been established for longer than 24-48 hours.

However, standard TEE probes and machines are large, cumbersome and very expensive. Placement of the TEE probe may be contraindicated by esophageal or gastric pathology, and it may be impracticable to provide repeated TEE imaging, especially at night. Recently a miniaturized (nasogastric tube sized), disposable monoplane TEE probe has been developed that provides continuous bedside TEE monitoring for up to 72 hours.\(^{39}\) This may be very helpful in the rapid and repeated assessment of acute perioperative hemodynamic derangements, hypovolemia, LV and/or RV failure, cardiac tamponade, and, because it incorporates color Doppler imaging, valve dysfunction. Its integration into ongoing goal-directed therapy has led to this modality being referred to as hemodynamic TEE or hTEE. Further refinements may ultimately offer many of the benefits of intraoperative TEE at the bedside.

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Non-Invasive Cardiac Output Monitoring: Ready For Prime-Time?

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LEARNER OBJECTIVES

After participating in this activity, the learner will be able to:

1. Identify the various means of non-invasive cardiac output monitoring;
2. Recognize the limitations of non-invasive cardiac output monitoring; and
3. Be aware of the clinical utility of non-invasive cardiac output monitoring in comparison with pulmonary artery catheterization and transesophageal echocardiography.

An historic quote from the 1834 London Times may illustrate how an ingenious instrument such as the stethoscope was initially underestimated:

“... that it will ever come into general use ... is extremely doubtful, ... because its beneficial application requires much time and gives a good bit of trouble both to the patient and the practitioner ... and because (it is) foreign and opposed to all our habits and associations.”

Although Pulmonary artery catheters (PAC) have long been the clinical gold standard for tracking hemodynamic variability in high-risk surgical patients, the true “gold standard” for the measurement of cardiac output (CO) is the Fick method. While the Fick method is clinically impractical, PACs permit the intermittent or continuous determination of CO as a key variable in the treatment of the cardiovascular system. Advanced cardiovascular monitoring and trending is an essential component of hemodynamic optimization of the perioperative patient and the critically ill. Recent evidence suggests that an individualized hemodynamic optimization is associated with both, reduced morbidity and intensive care unit length of stay. One of the primary goals of this hemodynamic optimization is the prevention of inadequate tissue perfusion and oxygenation. While PACs have been shown to provide reliable and continuous information with a reasonable response time, the have also been associated with significant cost and inherent risk due to their invasiveness. Furthermore, CO measurements made with the PAC are not as accurate as with the Fick method. Over the last several years, less or non-invasive continuous CO monitors have emerged as reasonable alternative. These non-invasive CO monitors should be reviewed by considering the following characteristics for CO monitoring techniques; accuracy, reproducibility or precision, rapid response time, operator independency, ease of use, continuous use, cost effectiveness, and no increased mortality and morbidity. This text briefly describes the various non-invasive methods to measure CO and discusses some of their individual advantages and disadvantages.

ARTERIAL PULSE CONTOUR METHODS

The estimation of CO based on pulse contour analysis is an indirect method, since CO is not measured directly, but is computed from an area under the curve of a pressure pulsation. The pulse contour method for estimation of beat-to-beat stroke volume goes back to the classic Windkessel model as described by Otto Frank in 1899 when he published his mathematical formulations. Most pulse contour methods are, explicitly or implicitly based on this model. They relate an arterial pressure or pressure difference to a flow or volume change. Currently, several pulse contour methods are available: the PiCCO (Pulsion Medical Systems), PulseCO™ (LiDCO Ltd., London, UK) and FlowTrac-Vigileo (TNO/BMI). All these three pulse contour methods use an invasively measured arterial blood pressure. Two of these three systems require calibration: PiCCO is calibrated by transpulmonary thermodilution, LiDCO by transpulmonary lithium dilution. The FlowTrac-Vigileo system relies on self-calibrating software and includes a proprietary algorithm that represents interplay of patient demographics, compliance of the arterial vasculature, and the rapidly changing nature of vasomotor tone. While the FloTrac-Vigileo initially has been embraced as a user-friendly CO monitor, recent validation studies suggest that only a minority of studies demonstrates acceptable limits of agreement (e.g. < 30%). In particular, a number of concerns have been raised regarding the ability of the earlier generations of this device to respond in a timely and accurate manner to rapid changes in peripheral vascular resistance during high-risk surgical procedures.

Another non-invasive pulse contour development is the combination of non-invasively measured arterial finger blood pressure with Modelflow (TNO/BMI). The Nexfin (BMEYE, Amsterdam, The Netherlands) is a newer device that has recently been introduced into practice. It provides beat-to-beat stroke volume and CO measurements by analysis of a non-invasive finger arterial blood pressure trace, derived continuously from an inflatable finger cuff. A recent study in 40 patients by Broch et al. suggests that this method correlates reasonably well with transcardiopulmonary thermodilution in cardiac surgery patients.

To what degree pulse contour CO monitors are able to trend CO over time remains a matter of debate. In direct comparison with esophageal Doppler CO, the pulse contour methods do not fully compensate for changes in peripheral vascular resistance and other...
circulatory changes while Doppler readings appear to be less affected.\textsuperscript{15}

Even though arterial pulse contour methods may not be quite as accurate as the true gold standards, they still have significant advantages. These include, but are not limited to, their minimal invasiveness, their response-time (beat-to-beat), and their ability to predict changes in CO and ultimately to track changes.

**INDICATOR DILUTION TECHNIQUES**

Indicator dilution techniques rely on the injection of an inert, soluble indicator substance into the circulation. Commercially available systems include the transpulmonary thermodilution (PiCCO, Pulsion Medical Systems), the transpulmonary lithium dilution method (LiDCO Ltd., London, UK) and the PAC based continuous thermodilution methods (Vigilance, Baxter; Opti-Q, Abott; and TruCCOMS, AorTech). Essentially all transpulmonary indicator dilution methods are modifications of the conventional intermittent bolus thermodilution method. CO is calculated based on the Steward method and the Hamilton modification.\textsuperscript{16} The Steward-Hamilton equation is based on the assumption that a) the injected indicator and the blood mix completely, b) that there will be no actual loss of the indicator between the place of injection and place of detection and c) that there is constant blood flow.\textsuperscript{17} Sources of error and variability include loss of indicator before, during or after injection, variation of the injectate temperature and/or volume and recirculation or detainment of indicator.

**FICK PRINCIPLE USING CARBON DIOXIDE**

The NICO (Novametrix) systems is a non-invasive device that applies Fick’s principle on carbon dioxide (CO\textsubscript{2}) and relies on a partial rebreathing technique and airway gas measurement. The systems calculates effective lung perfusion based on the evaluation of CO\textsubscript{2} elimination through integration of the measured gas flow and CO\textsubscript{2} concentration every 3 minutes after a brief period of partial rebreathing. The monitor requires the patient to be intubated. Individual ventilation/perfusion mismatch and the lack of an opportunity for calibration may explain why the accuracy of this method is mixed and why there is a lack of agreement between thermodilution and CO\textsubscript{2}-rebreathing CO.

**BIO-IMPEDANCE METHOD**

The continuous measurement of thoracic electrical bio-impedance (TEB) obtains an informative waveform signal: the portion of the bio-impedance waveform related to the cardiac cycle resembles to a large degree an arterial pressure waveform. For five decades, efforts were undertaken to derive stroke volume and CO of this waveform or its derivatives. These efforts relied on a model that contributes the rapid change of bio-impedance which occurs shortly after aortic valve opening to the expansion of the compliant ascending aorta, assuming that more blood volume temporarily stored in the ascending aorta contributes to a decrease in bio-impedance (or an increase in electrical conductivity of the thorax). Most current bio-impedance systems determine CO on a beat-to-beat time base. Excessive lung water (e.g. pulmonary edema) and acute changes in peripheral vascular resistance may negatively affect the reliability of CO measurements. This may help to explain relatively poor correlations when bio-impedance monitors are compared to a reference method in the critically ill or in septic patients.\textsuperscript{18} Persistence in marketing the bio-impedance method as a low-cost non-invasive approach to calculating CO, paired with the development of newer technologies, has resulted in a recent renaissance of these monitors.

**TRANSESOPHAGEAL ECHOCARDIOGRAPHY AND ULTRASOUND TECHNIQUES**

Transesophageal echocardiography (TEE) represents a clinical monitor that can assist the experienced anesthesiologist in the hemodynamic evaluation and management of surgical patients during general anesthesia. Hemodynamic evaluation with echocardiography consists of both, the qualitative and quantitative assessment. While qualitative assessment includes the description of chamber sizes and shapes, the quantitative approach to TEE allows the determination of blood flow and volumes, pressure gradients, valve areas and intracardiac pressures. Stroke volume (SV) can be calculated knowing the velocity time integral (VTI) and the cross sectional area (CSA) at the point where the VTI was determined. Most commonly, the left ventricular outflow tract (LVOT) is used to calculate echo-based SVs. The CSA equals πr squared, which can be substituted by 0.785 x diameter squared. This leads to:

\[
SV (\text{ml}) = CSA (\text{cm}^2) \times VTI (\text{cm/beat})
\]

Applied for the LVOT:

\[
\Rightarrow SV = 0.785 \times (\text{diameter LVOT})^2 \times VTI_{LVOT}
\]

**Cardiac output (CO)**

CO (l/min) = SV (ml) x HR (heart rate/min)

And applied for the LVOT:

\[
\Rightarrow CO = SV_{LVOT} (\text{ml}) \times HR (\text{beats/min})
\]

\[
\Rightarrow CO = 0.785 \times (\text{diameter LVOT})^2 \times VTI_{LVOT} \times HR
\]

TEE-based CO estimations have been compared to thermodilution techniques under varying conditions. While a large number of studies suggest that TEE based CO measurements have acceptable agreement and accuracy compared with thermodilution using the PAC\textsuperscript{19,21}, other studies have questioned this accuracy, especially in certain subgroups of patients.\textsuperscript{22,23} Of note, accurately estimating CO based on TEE and Doppler quantification requires a significant level of skills.

New developments in 3D echocardiography along with available 3D quantification software utilizing semi-automated endocardial border detection permit
fast and accurate measurements of global and regional left ventricular (LV) function.\textsuperscript{24-26} Studies comparing MRI with 3D echocardiography for the assessment of LV mass and function show very good correlation and agreement that is superior to 2D echocardiography.\textsuperscript{27} This also holds true for real-time 3D transthoracic echocardiography (RT-3D-TTE) assessment of patients with cardiomyopathies or regional wall motion abnormalities secondary to myocardial infarction with abnormal LV geometry.\textsuperscript{28-30} Global LV function is assessed by 3D analysis of endsystolic and enddiastolic volumes, EF and stroke volumes, which can be used to calculate CO. In a recent perioperative study, we have demonstrated the feasibility, reliability, and validity of similar volumetric studies based on 3D-TEE of the right ventricle (RV).\textsuperscript{31} This work suggests that 3D-TEE can reliably represent the complex geometry of the RV and, therefore, may constitute a valuable tool for dynamic perioperative assessment of RV function, stroke volumes and CO.

Recent technologic advances in ultrasound crystals have resulted in new miniature Doppler probes positioned inside the esophagus with their echo window on the thoracic aorta for measuring aortic flow velocity. Aortic cross sectional area is assumed (CardioQ, Deltex) or measured simultaneous with 2D–echo (HemoSonic, ARROW). Of note, these technologies do not measure CO directly but rather estimate aortic blood flow. However, based on the continuity principle, a fixed relationship between aortic blood flow and CO is assumed to calculate CO. Roeck et al. showed that abrupt changes in CO are much better followed with esophageal Doppler systems than with the PAC based continuous CO monitors.\textsuperscript{32}

CONCLUSION
While a large number of methods for the assessment of CO exist, none combines all eight criteria discussed in the introduction (accuracy, reproducibility or precision, rapid response time, operator independency, ease of use, continuous use, cost effectiveness, and no increased mortality and morbidity). Pulmonary artery thermodilution, lithium dilution and transpulmonary thermodilution provide valid and reliable intermittent thermodilution measurement.\textsuperscript{33} In a recent perioperative study, we have demonstrated the feasibility, reliability, and validity of similar volumetric studies based on 3D-TEE of the right ventricle (RV).\textsuperscript{31} This work suggests that 3D-TEE can reliably represent the complex geometry of the RV and, therefore, may constitute a valuable tool for dynamic perioperative assessment of RV function, stroke volumes and CO.

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Ambulatory surgery continues to grow in popularity. Currently, 60% of all procedures performed in the United States are done on an ambulatory basis.\(^1\) Surveys report that postoperative pain is a greater concern for patients than surgical outcome, and optimization of analgesia after ambulatory surgery can improve patient satisfaction and quality of life.

**OPTIMIZATION OF ANALGESIA:**

**General anesthesia techniques**

- Recent studies have reported the possibility of reduced postoperative pain after ambulatory procedures with the use of a propofol based anesthetic versus a volatile based anesthetic.\(^2\) Some studies suggest that propofol may have analgesic properties and may also prevent opioid induced hyperalgesia in patients undergoing breast cancer surgery.\(^3\) However these findings are inconsistent, and the magnitude of effect is limited. Opioid use is not markedly reduced, and postoperative pain scores are only marginally decreased for a relatively brief duration (< 12 hrs).

- Intravenous infusions of lidocaine (1.5–3 mg/kg/hr) have resulted in impressive results after major abdominal surgery,\(^4\) and a meta analysis noted reduction in pain scores, nausea, ileus, and length of stay. However, use of lidocaine for less invasive procedures such as total hip replacement has been unimpressive. A recent RCT examined effects of iv lidocaine infusion for ambulatory surgery patients.\(^5\) Opioid use was reduced without affecting incidence of nausea. Pain scores were lower while in the PACU but not different between groups at home.

**REGIONAL ANESTHESIA TECHNIQUES**

**Single shot**

- A previous meta analysis has examined RCTs comparing GA with central neuraxial and peripheral nerve blocks for anesthesia.\(^6\) Central neuraxial techniques were mixed for comparative outcomes with lower pain scores and less nausea but a longer time until discharge from the ASU (mean of 35 min). In contrast, use of peripheral nerve blocks was generally superior with less pain and nausea, faster discharge, and greater patient satisfaction.

**CONTINUOUS PERINEURAL CATHETERS**

- These beneficial effects of peripheral nerve blocks can now be extended to the home for patients with the advent of perineural catheters with portable or disposable pumps. A meta-analysis has examined RCTs that compared perineural catheters dosed with local anesthetic vs saline.\(^7\) All groups had free access to systemic opioids. The perineural catheters with local anesthetics were clearly superior with lesser pain scores at rest and activity for 48 hrs after surgery. The active catheters had reduced opioid use with reduction in nausea, sedation, and pruritus.

- Several clinical studies have also reported other benefits with use of perineural techniques for ambulatory surgery. A RCT examined effects of perineural analgesia versus IV PCA at home after ambulatory surgery.\(^8\) Perineural analgesia (interscalene or popliteal catheters) improved pain control, reduced opioid related side effects, and significantly increased patients’ ability to perform activities of daily living at home.

**Alternatives to continuous catheters**

- Despite the above documented advantages, ambulatory use of perineural catheters may be underutilized due to concerns over staffing, equipment needs, and potential minor and major complications.\(^9\) Large scale surveys report relatively low incidences of major complications (<1%) but substantial incidences for technical (kinking, blocked, displaced) complications and bacterial colonization (10–28%). Thus, interest has grown in the possibility of adding adjuncts to a single shot block in order to prolong effect and potentially obviate the need for a perineural catheter.

- Ultrasound guidance: A recent systematic review analyzing RCTs that compared ultrasound guided peripheral nerve blocks versus other guidance techniques (mostly nerve stimulator) found some evidence for prolonged sensory duration perhaps due to improved deposition of local anesthetic.\(^10\)

- Dexamethasone: Several RCTs have documented prolongations of peripheral nerve blocks with addition of dexamethasone (~8mg) to mepivacaine (332 vs 228 min), ropivacaine (22.2 vs 11.8 hrs), and bupivacaine (22.4 vs 14.8 hrs).\(^11,12\) Mechanism of prolongation is unknown.

- Buprenorphine: A recent RCT noted that addition of buprenorphine (0.3 mg) prolonged sciatic block with bupivacaine.\(^13\)
POSTOPERATIVE MULTIMODAL SYSTEMIC ANALGESIA

- NSAIDs: Meta analyses indicate that NSAIDs, especially in multiple doses, are highly useful analgesic adjuncts. They consistently reduce pain scores, reduce opioid use and opioid related side effects. However, prolonged use of NSAIDs is associated with cardiovascular risk, renal impairment, and increased bleeding for some surgical procedures (tonsils). Combining acetaminophen with NSAIDs provides further analgesia as documented by a separate qualitative meta-analysis. A recent meta analysis examined a small number of RCTs to determine effects of a single dose of perioperative ketorolac on postoperative analgesia and opioid related side effects. This meta-analysis also noted mild reductions in pain scores, opioid use, and opioid related side effects with a single dose of ketorolac.

- Dexamethasone: Although commonly used to prevent PONV, a recent meta analysis of RCTs noted that dexamethasone (0.1–>0.2 mg/kg) also improved pain scores for as long as 24 hours and decreased opioid consumption. Furthermore, a recent RCT observed that administration of dexamethasone 0.1 mg/kg reduced opioid consumption and improved QoR40 scores after ambulatory gynecological laparoscopy.

- Ketamine: A recent meta analysis of 4,701 patients observed potential beneficial effects of ketamine. Opioid consumption was reduced and time to first analgesic increased and effects were greatest for patients with highest pain scores. PONV was less frequent but hallucinations were increased.

- Gabapentanoids: Several meta analyses reported benefits for gabapentin and pregabalin. These agents (primarily gabapentin) reduced pain scores, opioid consumption and related side effects, but somewhat increased risk of sedation and dizziness (NNH of 12-35).

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Genomic Medicine Why Do “Similar” Patients Have Different Outcomes?

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ABSTRACT
Genomic variation is an important factor in why supposedly “similar” patients react differently to drugs, have different disease course(s), and varying clinical outcomes. This review provides an update on concepts in modern genomic medicine with emphasis on clinically relevant study approaches, disease/drug pathway analysis, and recent pharmacogenomic findings. The application of genomic medicine and its importance for rapid diagnosis of disease causing agents, as well as its clinical application in human disease diagnosis/treatment and in cardiovascular disease are discussed. In addition to direct clinical applications, modern genomic approaches also play an important role in elucidating new mechanisms of disease. Finally, the role of the NIH national pharmacogenomics research network (PGRN) in codifying “bench to bedside” translation of genetic results that impact drug therapy will also be discussed.

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 between 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 spectroscopy 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 cheapest 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 cross-overs, 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 powerhouses 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 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 co-variants 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 hard to publish unless replication in a separate group of individuals and/or associated biologic changes can be reported in the same study.

**GWAS studies:** Genome wide association 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/genes 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 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 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 taken into account, 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 anti-microbial 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 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 vigorously.

**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 ABCC1 (ATP-binding cassette sub-family C member1) gene for patient outcome has recently been suggested. Another example is breast cancer where BRCA gene mutations are well known to increase risk of breast cancer in a subpopulation of patients, yet the majority of breast cancers without BRCA mutations remain difficult to categorize and, in the cases, treat. 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 disease to familial peripheral arterial calcification, blood coagulation, and cardiovascular drug action. Even chronic inflammation, known to be important in the acquisition and progression of cardiovascular disease, has been examined in terms of “inflammasome-mediated disease.” In this review, we highlight one example of a commonly used clinical genetics approach to two types of anti-coagulation.

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 starting dose for highly toxic drugs such as warfarin (coumadin) and use/efficacy of anti-platelet drugs such as clopidogrel. 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. Because the improved prediction has great potential to limit warfarin side-effects such as excessive bleeding and emergency room visits, genetic testing is becoming more routine as warfarin is initiated. For clopidogrel, an anti-platelet 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 anti-platelet 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 FDA recently put a black box warning so that clinicians would be aware to prescribe alternative anti-platelet drugs to the subset of patients who are non-responders. Only recently has genetic variability of the enzymes regulating metabolism of the active drug been also investigated as another source of variable clinical outcomes.

Transplantation: Because genetic variation exists in molecules regulating innate and adaptive immunity, organ transplantation has become an area where genetic approaches are becoming increasingly considered. Genetic variants in this setting can have important effects in both organ preservation (e.g. sufficient immunosuppression to prevent rejection) and drug side effects (e.g. limiting immunosuppression side-effects such as infection, metabolic derangements, and renal injury). These effects include immune system modulation as well as drug metabolism pathways (e.g. CYP3A5 for tacrolimus dosing). Taken together, effects on acute rejection, delayed graft function, long-term allograft dysfunction and mortality, post-transplant metabolic complications, and recurrent disease are affected by many known genetic variants, specific for each phase of transplantation long-term success. Genetic variants and mRNA profiling that can be used for screening purposes, as well as future visions for how genomics can add value in this unique area of medicine, have been summarized in several recent reviews.

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 taken into account 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 U.S., who participate in clinical genetics trials in various common, complex human diseases. Their findings are located on the PGRN website at the NIH (http://goo.gl/4w0M3) 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 is annotated so clinicians can understand strength of results and recommendations. Although this site is not meant to be used as 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 (CPIC), which is currently
a group of 6 medical centers who 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 mechanism. An example of this can be seen in alpha1-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 (NE). Among the 3 α1AR subtypes, 1αARs predominate in human vascular smooth muscle, particularly in resistant vessels. 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. 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.

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Neurologic outcome following traumatic brain injury is related to the extent of the primary insult and the incidence and duration of secondary insults. Complications that contribute to secondary injury of the central nervous system (CNS) include hypoxia, hypotension, hyper-/hypoglycemia, hyper-/hypocapnia, hyperthermia and intracranial hypertension. Monitoring of cerebral hemodynamics, cerebral oxygenation, neurochemistry, and neuronal function detect cerebral hypoxia and/or ischaemia and provide information to taper pharmacological and surgical treatment according to the individual status of the patient. A monitored (individualized) approach rather than rigid treatment protocols will reduce the consequences of secondary insults, decrease neuronal injury and neurological deficit associated with cerebral ischaemia and may improve long-term neurologic outcome.

As related to the remarks stated above, the most important end-points in the treatment of severely head injured patients are the control of intracranial pressure below 25 mmHg and a cerebral perfusion pressure (CPP) within the range of 60 - 70 mmHg. Cerebral blood flow abnormalities frequently occur after traumatic brain injury and require individualized approaches in managing CPP: Currently, two different CPP management strategies (philosophies) attempt to maintain cerebral perfusion at a level adequate to fuel the cerebral metabolic needs. Although both of these concepts differ with respect to the level of CPP either of them may be appropriate depending of the individual status of CBF autoregulation and the blood-brain-barrier.

1. Cascade of cerebral vasodilation and vasoconstriction (“Rosner concept”, “Edinburgh concept”): Studies in patients with severe head injury have shown that hypotension and low CPP are important factors in the generation of secondary insults. For example, the incidence, severity, and duration of arterial hypotension or CPP <80mmHg significantly increased morbidity and mortality in these patients. The CPP approach requires intact cerebrovascular autoregulation in order to induce autoregulatory vasoconstriction for ICP control (i.e. as autoregulation is intact, elevations in CPP will produce autoregulatory vasoconstriction to maintain CBF normal while reducing intracranial blood volume and thus ICP; “Rosner concept”). This concept also applies to patients with a shift of the autoregulatory curve towards higher pressures (i.e. with “normal” CPP these patients present pressure-passive perfusion while elevations in CPP return their pressure-flow-relationship into the autoregulatory range; “Edinburgh concept”). These considerations are consistent with data in head injured patients showing fewer events with critical intracranial hypertension (plateau waves) as long a CPP was maintained with the range of 75-95 mmHg. However, target CPP values > 70 mmHg is associated with an increased risk for ARDS.

2. Treatment of posttraumatic brain edema formation (“Lund concept”): This approach assumes defective blood-brain barrier and cerebrovascular autoregulation. As a consequence the Lund concept targets at low precapillary hydrostatic pressures and cerebral venous constriction to reduce edema formation and elevated cerebral blood volume by infusion of a) dihydroergotamine (DHE), b) the alpha-2-agonist clonidine and the beta-1-antagonist metoprolol, and c) normalization of colloidosmotic pressure (plasma albumin concentration > 40 g/l). Although there may be subgroups of patients that benefit from a reduction in precapillary hydrostatic pressure along with cerebral venous constriction there are currently no convincing data that support improved outcome with the “Lund concept”. However, target CPP values < 50 mmHg are associated with an increased risk for cerebral ischemia.

If CPP 60 - 70 mmHg is available with excessive use of volume or vasopressors only, CPP of 50 mmHg is acceptable to avoid ARDS. All of the above interventions/goals infer that meticulous systemic and brain monitoring will be performed by experts. Likewise, thresholds for intervention need to be identified for every single monitoring technique. The final therapeutic goal is reflected in the algorithm as listed below:

Basic support and management:
1. Normoxia (PaO₂ ~ 100mmHg, SaO₂ > 96 %)
2. Normovolemia (SvO₂ > 70 %, avoid hypoosmolality)
3. Normotension (volume management)
4. Normocapnia (paCO₂: 36-40 mmHg)
5. Normoglycemia (in truth: permissive mild hyperglycemia to avoid hypoglycemia while infusing insulin; plasma glucose concentration: 120-150 mg/dl)
6. Normothermia (cool in desperate situation to control for ICP, strictly avoid hyperthermia)
7. Surgical decompression of space occupying lesions
8. Sedation

If maintenance of physiological variables within the normal range is inadequate to control for the above end-points, the following interventional support - despite lack of evidence - will be initiated based on expert opinion:

1. CSF-drainage
2. Barbiturate coma
3. Vasopressors
4. Osmodiuretics (mannitol, hypertonic saline)
5. Hyperventilation (paCO2: 30 mmHg),
6. TRIS-buffer
7. Mild hypothermia
8. Surgical decompression with dural patch
LEARNER OBJECTIVES

After participating in this activity, the learner will be able to:

1. Identify procedures and system changes for improving outcomes in obstetric hemorrhage;
2. Explain procedures and rationale for intrauterine resuscitation;
3. Identify systems for defining urgency of unscheduled cesarean deliveries (decision to delivery interval); and
4. Explain the rationale for various anesthesia care plans for urgent deliveries.

IMPROVING OUTCOMES IN OBSTETRIC HEMORRHAGE

Postpartum hemorrhage (PPH) is defined as > 500 mL blood loss after a vaginal delivery, and > 1000 mL blood loss after a cesarean delivery. PPH is a leading cause of maternal death, both in first and third world countries. The incidence appears to be increasing.\(^1\) Reviews suggest that many deaths from PPH are preventable. For example, 93% of PPH maternal deaths in the State of North Carolina between 1995 and 1999 were judged preventable.\(^2\) Outcomes may be improved by designing and implementing systems to assist providers in the timely recognition and treatment of PPH.

Ensuring the ready availability of blood products is critical to the resuscitation of the hemorrhaging patient. The American Society of Anesthesiologists 2007 Practice Guidelines for Obstetric Anesthesia recommend that a Type & Screen, or Type & Crossmatch should be based in maternal history and anticipated hemorrhagic complications.\(^3\) Unfortunately, a large number of women who hemorrhage do not have risk factors for PPH. At Northwestern Memorial Hospital in Chicago, IL, we have developed a Blood Bank Specimen protocol. The antibody status of most women is assessed during routine antenatal care. Therefore, parturients who are antibody negative and are at low risk of hemorrhage have a sample sent to the Blood Bank on admission, but the sample is not processed (so-called Draw & Hold). Parturients with a diagnosis that is associated with a high risk of hemorrhage (e.g., placenta accreta) receive a Type & Crossmatch on admission. Women with an intermediate risk receive a Type & Screen (e.g., all intrapartum cesarean deliveries). Women who are known to be antibody positive, or have received Rho(D) immune globulin (Rhogam) during pregnancy, have a high likelihood of a positive antibody screen, and therefore, by protocol, receive a Type & Screen on admission.\(^4\) This allows the Blood Bank to identify the antibody shortly after admission in case blood products are needed to treat PPH.

As a group, parturients are young, healthy, and hypervolemic. They remain asymptomatic until they lose a large amount of blood. Thus, the diagnosis of severe PPH is often delayed, resulting in suboptimal resuscitation. Additionally, studies have shown the providers are poor estimators of blood loss, especially when the blood loss is large (> 1 L). In a study using common materials encountered on a Labor & Delivery Unit (e.g., laparotomy sponge, perineal pad, delivery drape) and simulated blood loss, providers (obstetricians, anesthesiologists and nurses) averaged 38% underestimation of blood loss (Fig. 1).\(^5\) After completing an education module, the underestimation improved to 4%. Unfortunately, blood loss estimation skills had decayed after 9 months, demonstrating that education must be ongoing.\(^6\)

![Figure 1. Accuracy of pretest (top) and posttest (bottom) blood volume estimations compared to the actual value. The box represents the IQR, the line represents the median, and the whiskers represent 10th and 90th percentiles. Training modules were live (open boxes) or web-based (hatched boxes). \(\dagger\)different between live and web-based training; \(P < 0.05.\)

Successful resuscitation of hemorrhaging obstetric patients requires a team approach. Teams work together more efficiently and effectively if roles are defined ahead of time, and protocols are defined such that tasks are completed routinely and automatically. At Northwestern Memorial Hospital we have developed a PPH Protocol that defines roles/tasks for the primary nurse, secondary nurse, obstetrician, and anesthesiologist.
The protocol is in a checklist format and is based in the severity of PPH. Several organizations, including the World Health Organization (http://goo.gl/7yNjn) and the State of California (http://goo.gl/Ujxth) have promoted this type of protocol. An additional component of successful resuscitation of the hemorrhaging patient is a critical (or massive) blood loss protocol. Such a protocol allows the Blood Bank to issue large amounts of blood products quickly.7

Clinicians have questioned whether cell salvage can be safely used in obstetric hemorrhage as there is concern about whether amniotic fluid suctioned off the surgical field will result in an iatrogenic “amniotic fluid embolism.” Several in vitro studies, however, have demonstrated that blood suctioned off the field, washed, and then administered through a leukocyte-reducing filter, is safe to transfuse to a hemorrhaging patient.5,8 Clinical studies also suggest that cell salvage is a safe option in obstetric hemorrhage.10 Therefore, the use of cell salvage should be considered in the setting of massive obstetric hemorrhage.

INTRAUTERINE RESUSCITATION

Updated guidelines for the interpretation of fetal heart rate (FHR) tracings were published in 2008 (Box 1).11 Category 1 FHR tracings are normal, Category 2 tracings are indeterminate, and Category 3 tracings are abnormal. Normal uterine activity is defined as ≤ 5 contractions in 10 min, averaged over a 30-min window. Tachysystole is defined as > 5 contractions in 10 min, averaged over a 30-min window.

<table>
<thead>
<tr>
<th>Three-Tier Fetal Heart Rate Interpretation System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category I</td>
</tr>
<tr>
<td>Category 1 fetal heart rate (FHR) tracings include all of the following:</td>
</tr>
<tr>
<td>- Baseline rate: 100–160 beats per minute (bpm)</td>
</tr>
<tr>
<td>- Baseline FHR variability: moderate</td>
</tr>
<tr>
<td>- Late or variable decelerations: absent</td>
</tr>
<tr>
<td>- Early decelerations: present or absent</td>
</tr>
<tr>
<td>- Accelerations: present or absent</td>
</tr>
<tr>
<td>Category II</td>
</tr>
<tr>
<td>Category II fetal heart rate (FHR) tracings include all FHR tracings not categorized as Category I or Category III. Category II tracings may represent an appreciable fraction of those encountered in clinical care. Example of Category II FHR tracings include any of the following:</td>
</tr>
<tr>
<td>Baseline rate:</td>
</tr>
<tr>
<td>Baseline FHR variability:</td>
</tr>
<tr>
<td>- Minimal baseline variability:</td>
</tr>
<tr>
<td>- Absent baseline variability not accompanied by recurrent decelerations</td>
</tr>
<tr>
<td>- Marked baseline variability:</td>
</tr>
<tr>
<td>Accelerations:</td>
</tr>
<tr>
<td>- Absence of induced accelerations after fetal stimulation</td>
</tr>
<tr>
<td>Periodic or episodic decelerations:</td>
</tr>
<tr>
<td>- Recurrent variable decelerations:</td>
</tr>
<tr>
<td>- Periodic deceleration: 12 minutes × 30 minutes</td>
</tr>
<tr>
<td>- Recurrent late decelerations with moderate baseline variability</td>
</tr>
<tr>
<td>- Variable decelerations with other characteristics, such as slow return to baseline, “shoulder,” or “shoulder”</td>
</tr>
<tr>
<td>Category III</td>
</tr>
<tr>
<td>Category III fetal heart rate (FHR) tracings include:</td>
</tr>
<tr>
<td>- Absent baseline FHR variability and any of the following:</td>
</tr>
<tr>
<td>- Recurrent late decelerations:</td>
</tr>
<tr>
<td>- Recurrent variable decelerations:</td>
</tr>
<tr>
<td>- Bradycardia:</td>
</tr>
<tr>
<td>- Sustained pattern:</td>
</tr>
</tbody>
</table>

Box 1. 2008 National Institute of Child Health and Human Development: update on electronic fetal monitoring.11

Intrapartum fetal bradycardia requires intrauterine resuscitation. Clinicians have noted a temporal association between the initiation of neuraxial labor analgesia and fetal bradycardia. Although the mechanism is unclear, it has been suggested that it is related to the acute decrease in circulating epinephrine levels that occur shortly after the initiation of analgesia.12 Epinephrine, via its β2-adrenergic agonist activity, is a tocolytic, and an acute decrease may be associated with an increase in uterine tone, or even tachysystole. Because the uterus is perfused during uterine diastole, an increase in tone causes a decrease in uteroplacental perfusion, leading to fetal hypoxemia and bradycardia.

The reported incidence of neuraxial analgesia-associated fetal bradycardia is 2% to 30%. For example, in a randomized controlled trial (RCT) of the incidence of fetal bradycardia in epidural vs. combined-spinal epidural (CSE) analgesia, the overall incidence of prolonged fetal heart rate decelerations or bradycardia in the first 15 min was 19% (15/77).13 In contrast, in a prospective study of early vs. late labor initiation of neuraxial analgesia, the incidence of new onset non-reassuring fetal heart rate tracing in the first hour after CSE analgesia was 4.1% (15/362).14 Data are conflicting as to whether the risk of fetal bradycardia is higher after CSE than epidural analgesia. Fortunately, the risk of emergency cesarean delivery does not appear to be increased. In a retrospective study, the incidence of emergency cesarean delivery after CSE analgesia was 1.3% compared to 1.4% after administration of systemic analgesia.15

Intrauterine resuscitation should improve oxygen delivery to the fetus by increasing the oxygen content of fetal blood or ameliorating umbilical cord compression. Components of in utero resuscitation include 1) checking maternal blood pressure and treating hypotension, 2) changing in maternal position, 3) IV fluid bolus, 4) discontinuation of exogenous oxytocin infusion, 5) maternal oxygen therapy, and 6) tocolytic drug administration.

Maternal oxygen administration: Fetal oxygen content can be improved by increasing the maternal:fetal pO2 ratio. Using fetal pulse oximetry, investigators have demonstrated that the administration of oxygen to the mother increases fetal oxygen saturation (FSpO2); the lower the baseline FSpO2, the greater the effect of maternal oxygen administration.16,17

IV fluid: Investigators studied the effect of an IV fluid bolus in 42 parturients immediately prior to the initiation of neuraxial analgesia (Fig. 2).16 The infusion of
1-L lactated Ringer’s solution over 20 min resulted in a significant increase in FSpO₂, (mean 44.8% to 51.1%). This increase was not observed after the infusion of 500 mL.

Change in maternal position: Investigators also demonstrated that placing women in the left or right lateral compared to supine with a 30° head-up position, resulted in an increase in FSpO₂ (supine 37.5% ± 9.3, left lateral 48.3% ± 7.8, right lateral 47.7% ± 9.4; P < 0.03).

Treatment of uterine tachysystole increases uterine blood flow. The half-life of exogenous oxytocin is about 3 minutes; therefore, discontinuing the oxytocin infusion frequently results in resolution of tachysystole. If not, a tocolytic drug is usually administered. In a RCT of terbutaline (250 μg IV) vs. nitroglycerine (400 μg IV), there was no difference in rate of successful intrapartum fetal resuscitation (terbutaline 72%, NTG 64%; 95% CI of difference -9% to 2%).

In a 3-month, year 2000 prospective audit of 13 academic medical centers including prolapsed umbilical cord, placental abruption or previa with hemorrhage, or uterine rupture resulted in delivery within 30 min, but only 62% were delivered within 30 minutes if the indication of non-reassuring fetal status. In a 3-month, year 2000 prospective audit of all deliveries in Wales and England, only 16% of Grade 1 cesarean deliveries (immediate threat to life of woman or fetus) achieved a DDI < 15 min, and 46% < 30 min. Thus, it appears all but impossible, no matter the environment, to routinely achieve a DDI or DDI < 30 min for all intrapartum cesarean deliveries.

There are obviously some situations in which time is of the essence. For example, in a study of women with placental abruption and fetal bradycardia, a DDI < 20 min, compared to 20 – 30 min, resulted in a significantly smaller proportion of neonates with poor outcome (neonatal death or cerebral palsy) (odds ratio 0.44 (95% CI 0.22 – 0.86)). However, for most maternal-fetal dyads, and most indications of intrapartum cesarean delivery, fetal outcome is not related to DDI or DII. In the 2000 Wales-England audit, the 95% CI of the adjusted odds ratio of 5-min Apgar score < 7 (using DDI < 15 min as the reference) was not greater than one until the DDI exceeded 75 min (aOR 1.7 (95% CI 1.2 to 2.4)).

Thus, it makes sense to prioritize intrapartum cesarean deliveries by indication. Emergencies should be started as fast as possible (e.g., less than 15-min), while other procedures (e.g., arrest of labor with a Category 1 FHR tracing) can safely wait longer than 30 min, if necessary. Lucas et al. presented 10 intrapartum cesarean scenarios to 60 obstetricians and 30 anesthesiologists and asked them to use several different classification methods (e.g., visual analogue scale, suitable anesthetic technique, maximum DDI) to rate the scenarios. Clinical definitions were the most useful. The clinical scale was then applied to 407 actual cesarean cases in 6 hospitals. There was close agreement among the obstetricians and anesthesiologists; the 4-point scale had a weighted kappa of 0.91.

At Northwestern Memorial Hospital, we have developed a 4-category system. The obstetrician must “grade” the cesarean when he or she makes the decision to proceed with an intrapartum cesarean delivery (Box 2). The “grade” is documented in the medical record. It assists the nursing staff and anesthesiologists with prioritizing cases, and is also used as a quality management tool.

The attending physician making the decision to deliver the patient by an unscheduled cesarean will assign a priority grade to the case and communicate this to the L&D charge nurse and attending anesthesiologist.

1. **Grade 0**
   a. Clinical status allows for provider availability and compliance with hospital NPO protocol guidelines. Fetal heart rate status Category 1.
   b. Examples: include: planned cesarean birth with ruptured membranes; very early labor; oligohydramnios; mild preeclampsia or other stable indications for delivery.

2. **Grade 1**
   a. Clinical status allows for provider availability but may not allow for compliance with hospital NPO protocol guidelines. Fetal heart rate status Category 1.
   b. Examples: include: Arrest of labor; arrest of descent; active genital herpes with ruptured membranes; planned repeat cesarean with prior classical incision or cavity-entering myomectomy in labor; severe preeclampsia.

3. **Grade 2**
   a. Clinical status may allow for provider availability. Maternal or fetal compromise is not immediately life threatening. Fetal heart rate status Category 2 or Category 3.
   b. Examples: include: Arrest of labor; arrest of descent; planned cesarean delivery of an HIV positive patient in labor.

4. **Grade 3**
   a. Critical threat to life of the woman or fetus and immediate delivery indicated (crash / emergent). Fetal heart rate status Category 2 or Category 3.
   b. Examples: include: Maternal hemodynamic instability due to hemorrhage (e.g. placenta previa, abruptio placenta, uterine rupture); fetal emergencies including prolapsed umbilical cord.

Box 2. Intrapartum cesarean delivery grades at Northwestern Memorial Hospital, Chicago, IL.

**ANESTHESIA PLANS FOR URGENT DELIVERIES**

The induction of anesthesia for an urgent cesarean delivery must be performed quickly, but safely. Although recent data suggest that the maternal mortality gap between general and neuraxial anesthesia has narrowed in recent years, most experts still prefer neuraxial anesthesia if time allows. Many women in labor will have an in situ epidural catheter, and a sensory block from a dilute local anesthetic/opioid solution. Thus, quickly extending labor analgesia to surgical anesthesia is the technique of choice. Several
studies have investigated methods to shorten latency for surgical anesthesia.

**Chloroprocaine vs. lidocaine:** A small study compared 3% 2-chloroprocaine with sodium bicarbonate to 1.5% lidocaine with epinephrine 1:200,000 and sodium bicarbonate. A T4 sensory level to cold was achieved with a mean (SD) of 3.1 ± 0.3 min for chloroprocaine and 4.4 ± 1.6 min for lidocaine. Both drugs provided satisfactory analgesia. Thus, in a very emergent situation, there may be a clinical advantage to chloroprocaine, especially because the lidocaine solution must be mixed with epinephrine, and it is safer to administer large doses of chloroprocaine quickly.

**Addition of fentanyl:** Studies assessing whether the addition of fentanyl, 75 μg to 100 μg, shortens latency, are inconsistent. Hong et al. compared fentanyl to saline in a RCT in women who received 2% lidocaine with epinephrine 1:200,000 for cesarean delivery. Although there was no statistically significant difference in the onset of a T4 sensory level, the study was likely underpowered to show a difference (fentanyl group median 95% CI: 12.5 min (10.4-14.4), saline 15.0 min (13.5-16.5). However, the quality of analgesia was better in the fentanyl group, and there was less nausea.

In contrast, when fentanyl was added to 0.5% levobupivacaine for cesarean delivery, there was no difference in the onset time or quality of analgesia.

**Addition of sodium bicarbonate:** Alkalization of local anesthetic solutions increases the proportion of molecules in the unionized state, thus increasing movement across cell membranes. The addition of epinephrine (1.2 meq) to 15 mL premixed 2% lidocaine with epinephrine 1:200,000 with fentanyl 75 μg increases the pH from 4.3 to 7.4. The latency to a T6 sensory level to pinprick was shorter with sodium bicarbonate (mean 5.2 ± 1.5 (range 2-8) min vs 9.7 ± 1.6 (6-12) min; mean difference 4.5 min (95% CI 3.5 - 5.5). Similarly, the addition of sodium bicarbonate to 2-chloroprocaine shortened latency (sensory block to cold) (2.7 ± 0.8 min vs 4.2 ± 0.8 min).

**Spinal anesthesia:** Kinsella et al. described a case series in which “rapid sequence” spinal anesthesia was used to induce anesthesia for Category 1 (emergency) cesarean deliveries. Components of the technique include deploying other staff to obtain IV access, no skin infiltration, no opioid (increase bupivacaine dose to 15 mg), one attempt, preoxygenate and prepare for general anesthesia, and start surgical procedure when the sensory level is ≥ T10. Using this technique in 25 patients, three required general anesthesia, and three had breakthrough pain, although no supplementation was necessary.

**REFERENCES**


32. Lam DT, Ngan Kee WD, Khaw KS. Extension of epidural blockade in labour for emergency Caesarean section using 2% lidocaine with epinephrine and fentanyl, with or without alkalinisation. Anaesthesia 2001;56:790-4
OVERVIEW

Pain is a normal response to injury. There are specific anatomic and physiologic changes that ensue immediately following tissue damage that remind us to protect the injured area until the injury has healed. Normally, these changes abate as the tissue heals. But these same changes persist in some individuals long after all healing has occurred in the form of chronic pain. It is clear that a period of acute pain always precedes the development of chronic pain. But it is unclear what leads to persistent pain after injury in some individuals and complete healing without residual pain in others. Initial attempts to reduce postoperative pain and lower the chance of chronic pain took the form of administering analgesics “preemptively”, prior to the anticipated surgical insult. This approach has been disappointing. At the same time, we have come to learn that persistent pain after surgery or other traumatic injuries is surprisingly common after most common types of surgery. We are now starting to see trials of specific analgesic regimens aimed at preventing the transition from acute to chronic pain, examining patients at long term follow up. This refresher course lecture will review our current understanding of the anatomy and physiology of pain, discuss the extensive evidence that suggests that a preemptive approach to providing analgesia has proven disappointing, detail the specific risk factors that are linked with the development of chronic pain after surgery, and examine the current trends toward employing specific agents in the perioperative period aimed at reducing the incidence of chronic pain following surgery.

THE ANATOMY OF PHYSIOLOGY OF PAIN

Pain is defined by the International Association for the Study of Pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage”\(^1\). Pain is a normal, protective, physiologic response. Without pain, we are subject to repeated injury allowing injured areas to heal poorly or not at all. Diabetics who gradually lose sensation in their feet as the diabetic neuropathy progresses often develop skin ulceration. These areas heal poorly without the normal protective reminder that pain provides, often leading to amputation. Poorly healing decubitus ulcers that occur in patients who have sustained spinal cord injury are another example of the importance of normal sensation and pain in reminding us to protect injured areas so that healing can proceed without recurrent injury. Congenital insensitivity to pain is a rare condition where the affected person cannot feel physical pain. Affected individuals often develop severe infections after injury, as the initial injury goes unnoticed, eventually losing digits to recurrent injury and being subject to recurrent infections.

Much has been learned about the specific neural mechanism underlying the perception of pain and the response of the nervous system after injury. The specific neural mechanisms that lead from a harmful or potentially harmful stimulus to the perception of pain are collectively termed nociception. Nociception can be divided in to discrete events that together lead to the perception of pain (Figure 1). First, the actual or potential damaging stimulus must be converted to electrical impulses, a process known as transduction. Heat, cold, mechanical distortion, and changes in tissue pH are all stimuli that are potentially damaging to tissue and are converted to electrical impulses that travel toward the central nervous system along pain fibers. The primary organ of pain perception is the free nerve ending in the periphery. Free nerve endings convert these specific stimuli to neuronal impulses through changes in activity in specific ion channels within peripheral nerves. Following transduction, nerve pain signals travel as neuronal impulses toward the central nervous system along pain fibers. The primary afferent nociceptor

\(\text{Figure 1. Nociception. The neuronal events that lead to the perception of pain.}\)
along the nerve’s central projection that synapses on a second order neuron within the dorsal horn of the spinal cord. The second order neuron, in turn, sends a projection across midline to join the spinothalamic tract in the anterolateral aspect of the spinal cord. Pain signals travel cephalad in the spinothalamic tracts to reach the thalamus, the relay station which sends projection to the primary somatosensory cortex as well as various other regions within the brain. Incoming pain signals can be modulated or dampened. The endogenous opioid system acts in just this way: opioid agonists bind to receptors within the rostroventral medulla and the periaquaductal gray area of the brainstem and lead to an increase in descending inhibitory neuronal traffic that reaches that reaches the dorsal horn and reduces the amplitude of incoming pain signals. Thus, at the level of the dorsal horn where incoming nociceptive neuronal traffic enters the central nervous system, pain impulses can be modified in various ways. This is the sum of the processes that lead to the normal perception of pain.

When a barrage of nociceptive neuronal impulses reaches the dorsal horn, the activity in a specific group of second order neurons changes. Second order neurons fire more rapidly with subsequent activation (termed spinal cord wind up) and new connections develop between neurons that normally carry non-painful stimuli and those that carry pain signals. These changes in the dorsal horn are collectively called central sensitization. The net result of central sensitization is that the injured area becomes sensitized. While this sounds complex, the actual sum effect of these neuronal changes is something that we understand intuitively. Place your hand on a hot stove and you will immediately and reflexively pull your hand away from the damaging heat. Almost instantaneously after the injury, touching the area even lightly will produce a painful sensation rather than the non-painful sensation of light touch that was produced by the same stimulus before the injury. This pain to normally non-painful stimuli is termed allodynia, and it reminds us to protect the injured area until the injury has healed; sensitization is the neuronal mechanism that underlies the development of allodynia. Normally, allodynia disappears as tissue heals. But, in some individuals and after some types of injury, this sensitization persists even after all tissue healing appears to be complete in the form of neuropathic pain.

THE RISE AND FALL OF PRE-EMPTE ANALGESIA

Soon after the first detailed descriptions of central sensitization came the idea that blocking the barrage of nociceptive input to the dorsal horn at the time of injury might reduce the subsequent magnitude of acute pain and perhaps even reduce the likelihood of developing chronic pain. In the case of elective surgery, the location and time of the damaging tissue injury is known in advance. Thus, administering an analgesic “preemptively” prior to the surgical insult is feasible and perhaps doing so would reduce or eliminate the subsequent central sensitization by reducing the magnitude of the nociceptive input to the dorsal horn. This concept has been tested in dozens of randomized trials. Many different analgesics have been tested in this way, including non-steroidal anti-inflammatory drugs, opioid analgesics, peripheral local anesthetic infiltration, peripheral nerve blocks, and neuraxial techniques. In many such well-conducted trials, the analgesic was administered either before the surgical incision or after the surgical incision was made and patients’ subsequent pain experience was catalogued. There have been two recent meta-analyses that present the sum experience with preemptive analgesia in detail. While these two reviews reach different conclusions, a careful look at the underlying assumptions in the two analyses will lead the reader to the same conclusions. Statistical improvements in postoperative pain relief by preemptive treatment were seen at some time points in about one-third of the nearly 100 trials examined, however quantitative analysis of pain scores within 24 hours after surgery were in no case significant. Thus, there is lack of evidence for any robust preemptive analgesic effect across a wide range of different surgeries using many different analgesics and analgesic combinations. Indeed, the pain relief provided by a well-functioning epidural is just as good if the epidural is dosed at the conclusion of the surgery as compared with dosing the same epidural prior to the surgical incision. The authors of one of these articles suggested that future studies should redirect focus from timing to protective analgesia, aimed at preventing pain hypersensitivity, a concept that we will explore in some detail later in this review.

RISK FACTORS FOR THE DEVELOPMENT OF CHRONIC PAIN

Now let us turn for a moment to the other end of the healing process. Long after surgery, after all of the injured tissue appears to have healed completely, some patients are left with persistent pain. Numerous well-conducted population surveys are now available and they point to a disturbing conclusion. Persistent pain after surgery is common and, in a significant proportion of affected patients, the pain remains severe and disabling for months or years after surgery (Table 1).

Table 1 – Estimated incidence of chronic postoperative pain and disability after selected surgical procedures* (Reproduced from permission from reference 5).

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Estimated incidence of chronic pain</th>
<th>Estimated chronic severe (disabling) pain (score of 10)</th>
<th>US surgical volumes (1000s)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amputation</td>
<td>30-50%</td>
<td>5-10%</td>
<td>159 (lower limbs only)</td>
</tr>
<tr>
<td>Breast surgery (lumpectomy and mastectomy)</td>
<td>20-30%</td>
<td>5-10%</td>
<td>479</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>10-40%</td>
<td>5-10%</td>
<td>Unknown</td>
</tr>
<tr>
<td>Inguinal hernia repair</td>
<td>10%</td>
<td>2-4%</td>
<td>609</td>
</tr>
<tr>
<td>Coronary artery bypass surgery</td>
<td>30-50%</td>
<td>5-10%</td>
<td>598</td>
</tr>
<tr>
<td>Carasal section</td>
<td>10%</td>
<td>4%</td>
<td>220</td>
</tr>
</tbody>
</table>

*Gall bladder surgery not included, since preoperative diagnosis of pain specifically from gall bladder is difficult and persistent postoperative pain could therefore be related to other intra-abdominal disorders.
†National Center for Health Statistics, Ambulatory and Inpatients Procedures, USA, 1996.

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With the realization that chronic pain is common after tissue injury following trauma or surgical intervention of any kind, investigation turned toward examination of the underlying risk factors. A number of specific risk factors have been identified; among them are the magnitude of tissue injury, genetic factors leading to susceptibility to chronic pain, preceding chronic pain in any anatomic location, psychosocial factors, and age and sex (Figure 2). Much attention has been focused on modifying surgical techniques to minimize the extent of tissue injury; a turn toward endoscopic techniques with natural orifice transluminal endoscopic surgery being perhaps the ultimate development in this trend. Indeed, recent evidence has demonstrated that the incidence of persistent postsurgical pain following inguinal hernia repair is significantly lower than the incidence of persistent postsurgical pain following open technique.7 Clear and convincing evidence of the link between specific single nucleotide genetic polymorphisms and pain susceptibility has emerged. Indeed, we can now identify specific individuals who have low likelihood of severe pain following surgery and these same individuals are less likely than those without the same genetic profile to develop chronic pain.8 What is less clear is how to use this new information. Can we use preoperative genetic screening to effectively identify patients at high risk and somehow modify their management to minimize postoperative pain and the risk of developing chronic pain? This question remains unanswered and is the subject of intensive ongoing study.

FROM PREEMPTIVE TO PREVENTATIVE ANALGESIA

Extensive clinical trials have made it clear that simply providing analgesia before the surgical insult will not be enough to improve post-operative pain control or reduce the incidence of chronic pain. Why is preemptive analgesia insufficient? The precise reasons that our current approaches to providing preemptive analgesia are inadequate are unclear, but several hypotheses have emerged. The first is readily apparent. None of the many different approaches to providing preemptive analgesia can completely eliminate the barrage of nociceptive input from reaching and sensitizing the central nervous system. In the clinical realm, this is obvious. For instance, when we employ continuous epidural analgesia, the postoperative infusion is most often low-dose local anesthetic and opioid in combination. This provides excellent analgesia, but spares patients dense sensory and motor blockade that would limit movement and put them at risk for injury to the anesthetized areas. These patients still experience mild to moderate pain during their recovery. Thus, the central nervous system is still receiving nociceptive input and the central sensitization that is the normal physiologic process to injury still ensues. Thus, it seems unreasonable to expect that the processes that link acute pain to chronic pain have been unlinked. The second observation is that tissue injury leads to the production of circulating humoral mediators which enter the bloodstream and lead to sensitization of the central nervous system even when there is no direct neural traffic reaching the dorsal horn.7 So how do we move from the failed concept of preemptive analgesia to the adoption of analgesic regimens that are directly targeted toward the neural mechanisms that lead to severe acute pain and the chronic neural changes associated with chronic pain? There have been a number of promising recent studies that employed specific analgesic agents or combinations of analgesic agents and followed patients for long intervals after surgery, cataloguing their pain experiences and the incidence of chronic. Lavand’homme and colleagues randomized 85 patients undergoing elective colon resection to receive a multimodal regimen that included intra-operative ketamine, local anesthetic, clonidine, and opioid administered.
either intravenously or epidurally and then followed their postoperative course. Outcomes included long-term assessment of patients for persistent pain out to a year after surgery. None of the patients who had epidural analgesia intraoperatively had chronic pain requiring treatment at one year after surgery, while 12% of those who did not receive epidural analgesia had persistent pain requiring treatment at one year follow-up. In another well designed and conducted trial, Kumar and colleagues randomized 240 patients undergoing total knee arthroplasty to receive either placebo or oral pregabalin pre-operatively and for 14 days after surgery. None of those patients who received pregabalin reported chronic pain at 6 months after surgery, while 5.2% of those receiving placebo reported ongoing and significant pain at the surgical site. There are a number of other smaller, uncontrolled studies that also support the notion that short-term intervention in the perioperative period can impact the incidence of chronic pain, but these studies are nothing more than suggestive. What is clear from this work is that the impact of analgesic interventions must be assessed far beyond the postoperative period to assess their true value, and anesthesiologists are likely to be involved closely in these long-term outcome studies. The exact analgesic agents and the specific approaches to modifying the transition from acute to chronic pain will evolve swiftly in the years to come. Many risk factors are well-validated as predictors of the severity of acute pain following injury and the probability of chronic persistent pain. The challenge ahead is to determine what we can do to use this information to identify high-risk patients and modify their peri-operative treatment in ways that impact the development of chronic pain.

REFERENCES
Perioperative Lung Protection Strategies: Are They Worth the Trouble?

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INTRODUCTION
Patients are at risk for several types of lung injury in the peri-operative 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 PEEP can decrease the extent of this injury. This lecture will look at the effects of mechanical ventilation and its role in Ventilator Associated Lung Injury (VILI) with specific reference to Thoracic Anesthesia. The specific clinical scenarios of Chronic Obstructive Pulmonary Disease (COPD), One-lung ventilation, Cardio-pulmonary Bypass and Transfusion related lung injury (TRALI) will be examined. Newer work looking at lung protection strategies will briefly be discussed.

MECHANICAL VENTILATION
Historically, Anesthesiologists have been taught to ventilate patients in the peri-operative period with relatively large tidal volumes. Volumes as high as 15ml/kg ideal body weight have been suggested to avoid intra-operative atelectasis. This far exceeds the normal spontaneous tidal volumes (6ml.kg⁻¹) common to most mammals. Recent studies have identified the use of large tidal volumes as a major risk factor for development of lung injury in mechanically ventilated patients without acute lung injury (ALI). Gajic reported that 25% of patients with normal lungs ventilated in an ICU 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 have found that tidal volumes > 700mls and peak airway pressures > 30cm H₂O were independently associated with the development of ARDS. An intra-operative study of patients having oesophageal surgery compared the use of tidal volumes of 9 ml.kg⁻¹ without positive end-expiratory pressure (PEEP) during two- and one-lung ventilation vs. 9 ml.kg⁻¹ during two-lung ventilation and 5 ml.kg⁻¹ during one-lung ventilation with PEEP 5 cmH₂O throughout. They found significantly lower serum makers of inflammation (cytokines IL-1β, IL-6 and IL-8) in the lower tidal volume plus PEEP group. The study did not find any major difference in post-operative 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 one-lung ventilation, but not after 18h. In a study looking at conventional vs. protective ventilation in critically ill patients without lung injury, de Olivera and colleagues 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 post-ventilation, inflammatory markers in broncho-alveolar lavage fluid (TNFα and IL-8) were significantly higher in the larger tidal volume group. Choi and colleagues compared 12ml.kg⁻¹ without PEEP vs. 6ml.kg⁻¹ with 10cm PEEP and showed pro-coagulant changes in lavage fluid of the larger tidal volume group after 5 hours of mechanical ventilation. A recent randomised-control trial in 150 critically ill patients without ALI compared tidal volumes of 10ml.kg⁻¹ vs. 6ml.kg⁻¹ predicted body weight. The conventional tidal volumes were associated with a sustained plasma increase in inflammatory cytokines. Of importance is recent work suggesting that non-injurious or so-called protective ventilatory settings can induce lung injury in previously healthy lungs. An animal study using a very elegant murine ‘one hit’ ventilator induced lung injury (VILI) model, showed that even 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. A pig study suggested that ventilation with 15ml.kg⁻¹ and 3cmH₂O PEEP was less injurious than 6 ml.kg⁻¹ with either 3 or 10 cmH₂O PEEP.

ALI is the most common cause of post-operative respiratory failure and is associated with a markedly decreased post-op survival. A prospective case controlled study by Fernandez-Perez and colleagues looking at intra-operative ventilator settings and ALI after elective surgery in over 4000 patients showed a 3% incidence of ALI in high-risk elective surgeries. Compared with controls, patients with ALI had significantly lower postoperative survival and increased length of hospital stay. Interestingly in this study, intra-operative peak airway pressure, but not tidal volume, PEEP or FiO₂, were associated with ALI. A retrospective cohort study looking specifically at intra-operative 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). 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 were ventilated with...
a Vt.IBW\(^1\) of 8-10ml.kg\(^{-1}\) and an intra-operative PEEP of 0.

**VENTILATOR INDUCED LUNG INJURY (VILI)**

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.

The deleterious effects of mechanical ventilation may be mediated by localized inflammation and the systemic release of inflammatory cytokines (bio-trauma). Mechanical stretch from cycler alveolar opening and closing sets up an inflammatory response in the alveolar epithelial cells and the vascular endothelial cells. Hyperinflation causes nuclear translocation of NF-kB (a key regulator of the expression of multiple genes involved in inflammatory response) and up-regulation of other pro-inflammatory 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 ischaemia-reperfusion and mechanical stretch.\(^{15}\)

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 looking at 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.\(^{16}\) 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.\(^{17}\) These studies go some way as to explain the remote organ dysfunction seen with ALI/ARDS, and the role optimising ventilatory strategies play in ameliorating this.

This leads to the question; are the lung protective strategies in ARDS\(^18\) applicable to the peri-operative environment, specifically in patients with healthy lungs? A recent paper looking at this question highlights the lack of randomised-controlled trials looking at best intra-operative tidal volume, PEEP, and use of intra-operative lung recruitment.\(^{19}\) 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 peri-operative practice.

**PERI-OPERATIVE 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 vs. open techniques.\(^{2,22}\)

Atelectasis occurs frequently following open surgical procedures and in up to 90% of patients undergoing general anaesthesia.\(^{25}\) It is a pathological state that can contribute to or attenuate lung injury. Thus anaesthesiologists must be aware of techniques to avoid or treat it.\(^{24}\) While open to debate, retrospective\(^{25,26}\) and prospective\(^{27}\) 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.\(^{28}\) Reviews comparing Para-vertebral block (PVB)\(^{29,30}\) vs. epidural analgesia in patients undergoing thoracic surgery showed equivalent analgesia efficacy but a better side effect profile and lower complication rate with PVB. Aggressive physiotherapy with CPAP in the post-operative period in patients after major abdominal surgery who develop early desaturation leads to lower rates of major respiratory complications.\(^{31}\)

**PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)**

COPD patients are at an increased risk of lung injury in the peri-operative period.\(^{32}\) Key concepts that are relevant to anaesthetic management and lung protection include:

**Dynamic hyperinflation:** Emphysema is almost exclusively an expiratory disease, thus during positive pressure ventilation moving gas into the patient’s lungs is easy, but due to intrinsic PEEP (auto-PEEP) it is extremely difficult to move the gas out. This intrathoracic gas trapping is called dynamic hyperinflation.\(^{33}\) Severe hyperinflation impairs cardiac venous return leading to hypotension and in severe cases, cardiac arrest.\(^{34}\) This can occur during seemingly low levels of positive airway pressure, such as during bag-mask ventilation at induction. Anaesthesiologists must be very alert to this entity. Thorough pre-oxygenation prior to induction, use of small tidal volumes, slow respiratory rates with long expiratory times, tolerance of hypocarbia and hemodynamic support are key to avoiding hemodynamic collapse in these patients. Acute decompression during positive pressure ventilation of these patients presents a challenging differential diagnosis between dynamic hyperinflation and tension pneumothorax. Unilateral breath sounds, tracheal shift and presence of bullae favour pneumothorax and the need for urgent decompression. In the absence of these clues it is reasonable to disconnect the patient from the ventilatory circuit and allow passive exhalation to the atmosphere. If there is no improvement with a period
of apnoea, then treatment measures for pneumothorax should be instituted.

**Bullae:** Many patients with moderate to severe COPD develop cystic air spaces in the lung parenchyma. These bullae will tend to be asymptomatic unless occupying more than 50% of the hemi-thorax, in which case patients will have features of restrictive and obstructive lung disease. These bullae are localized areas of loss of structural support tissue in the lung with elastic recoil of surrounding parenchyma. The pressure in the bullae is the mean pressure in the surrounding alveoli averaged over the respiratory cycle. This means that during normal spontaneous ventilation the intra-bulla pressure is slightly negative in comparison to the surrounding parenchyma. When positive pressure ventilation is instituted the pressure in the bulla becomes positive in relation to adjacent structures and the bulla will expand, with the attendant risk of rupture, tension pneumothorax and bronchopleural fistula. Positive pressure ventilation can be safely used if airway pressures are kept low and there is the expertise and equipment available for chest drain insertion and lung isolation.

**Respiratory drive:** Determining patient’s PaCO₂ baseline with peri-operative arterial blood gases is important in setting goals for intra- and post-ventilation. It is not possible to predict which patients are CO₂-retainers based on severity of their disease. CO₂ retention seems primarily related not to an alteration of respiratory control mechanisms but due to an inability to maintain the increased work of respiration. In patients receiving supplemental oxygenation the PaCO₂ rises not due to decreased minute ventilation but due to a relative increase in alveolar dead space by the redistribution of lung perfusion and due to the Haldane effect. However, post operative hypoxemia must be prevented with supplemental oxygen; the attendant rise in PaCO₂ must be anticipated and monitored. Arterial blood gases and level of consciousness are the best monitors, with PaCO₂ levels of > 10-13kPa having sedative and anaesthetic effects.

**Nocturnal Hypoxemia:** COPD patients desaturate more frequently and severely than normal patients during sleep. This is related to the rapid shallow pattern of ventilation which occurs in all patients during REM sleep. This tendency to desaturate combined with the postoperative fall in FRC and opioid analgesia places these patients at high risk for severe hypoxemia postoperatively during sleep.

**Right ventricular dysfunction:** RV dysfunction occurs in up to 50% of COPD patients. A dysfunctional RV is intolerant of sudden changes in afterload associated with switching from spontaneous to controlled ventilation or large pulmonary resections.

**PERI-OPERATIVE THERAPY OF COPD TO DECREASE LUNG INJURY**

**Physiotherapy:** It has been clearly shown that patients with COPD benefit form an intensive program of preoperative chest physiotherapy, with fewer postoperative pulmonary complications. It is possible to improve exercise tolerance in even the most severe COPD patient. However, little improvement is seen before one month. Those COPD patients with excessive sputum production benefit the most from chest physiotherapy.

**Smoking cessation:** A pre-operative smoking cessation program can significantly decrease the incidence of respiratory complications (4-8 weeks abstinence), wound complications (4 weeks abstinence), and intra-operative myocardial ischemia (48h abstinence).

**Bronchodilation:** Broncho-constriction is assessed by history, physical examination and evaluation of pulmonary function response to bronchodilators. Patients should receive maximal bronchodilator therapy as guided by their symptoms. It is not clear if corticosteroids are as beneficial as they are in asthma, but in patients poorly controlled on sympathomimetic and anticholinergic bronchodilators a trial of corticosteroids may be beneficial. Pulmonary function tests are not useful screening tools for all patients, but are valuable in assessing flow rates in symptomatic patients, to confirm the diagnosis and to assess adequacy of treatment. Incidence of intra-operative life-threatening bronchospasm has become very low. The principles for managing patients with reactive Airways remains the same however: preoperative optimizing of bronchodilation, avoiding instrumentation of the airway, airway instrumentation at an adequate depth of anaesthesia, use of bronchodilating anaesthetics (volatiles, propofol, ketamine) and appropriate warming and humidification of gases. In patients with bronchial hyperactivity on regular bronchodilator therapy, post-intubation wheezing can be significantly reduced by a 5-day preoperative course of corticosteroids.

**ONE LUNG VENTILATION (OLV)**

Anesthesiologists are faced with a heterogeneous patient group, in terms of underlying pathology and surgical procedure, requiring one-lung ventilation. Both the patient’s pathology and the surgical procedure can predispose to or cause ALI. ALI following pulmonary resection has been described since the beginning of OLV for thoracic surgery. The most publicized report is a compilation of 10 pneumonectomy cases published in 1984 which focused on the role of intravenous overhydration as a cause of post-pneumonectomy pulmonary oedema. Much work has subsequently followed and our understanding of risk factors, mechanisms of injury and management strategies for what is now termed post-thoracotomy ALI has greatly advanced. A thorough retrospective study of 806 pneumonectomies found a 2.5% incidence of post pneumonectomy pulmonary oedema with a 100% mortality in affected patients. There was no difference in peri-operative fluid balance between post-pneumonectomy ALI cases (24 hr fluid balance 10ml.kg⁻¹) vs. matched pneumonectomy controls (13ml.kg⁻¹). Authors used rigorous fluid restriction compared to other reports, suggesting that limiting intra-operative fluids might
decrease but not eliminate ALI. Post-pneumonectomy pulmonary ALI has been shown to have a bimodal distribution of onset. Late cases presented 3-10 days post operatively and were secondary to obvious causes such as broncho-pneumonia, aspiration etc. Early or “primary” ALI presented on post-operative days 0-3. Four factors were independent significant predictors of primary ALI: high intra-operative ventilation pressures, excessive intravenous volume replacement, pneumonectomy, and pre-operative alcohol abuse. Looking specifically at ventilation pressures, Licker and colleagues used a baro-trauma index taking into account both duration of OLV and increased inspiratory pressure. This index represented the strongest risk factor for ALI (approximately threefold increase risk if PIP ≥ 25cm H₂O vs. PIP = 15cm H₂O). The known facts about ALI following lung surgery include: an incidence following pneumonectomy of 2-4%, greater frequency of right vs. left pneumonectomy, symptom onset 1-3 days post surgery, high associated mortality (25-50%), and resistance to standard therapies. While ALI occurs after lesser resections (e.g. lobectomy) it has a much lower mortality rate. Of note, in 8/9 cases who developed unilateral ALI following lobectomy, the ALI was in the non-operated (i.e. the ventilated) lung. While there is an association between postoperative ALI and fluid overload, the non-cardiogenic nature of the pulmonary oedema (low/normal pulmonary occlusion pressures) and the protein rich oedema fluid is much more in keeping with an ARDS type picture, with endothelial damage playing a key role. Post-operative increases in lung permeability of the non-operated lung have been demonstrated after pneumonectomy but not lobectomy. This capillary-leak injury may be due to an inflammatory cascade affecting even the non-operative lung that is triggered by lung resection and is proportional to the amount of lung resected.

Free oxygen radical generation in lung cancer patients is related to the duration of OLV. While there is no single mechanism to explain ALI post lung resection, a unifying hypothesis is that there is a spectrum of ALI that occurs during all lung resections; the more extensive the resection the more likely there is to be post-operative injury. End-inspiratory lung volume is a key factor in VILI. Many patients, especially emphysema patients, develop auto-PEEP with OLV, thus inspiration begins at a lung volume above functional residual capacity (FRC). Using large tidal volumes (10-12ml.kg⁻¹) during OLV in such patients produces end-inspiratory at levels that may cause or contribute to ALI. The effects of PEEP during OLV are variable and very much dependant on the lung mechanics of the individual patient, with initial studies suggesting that it leads to a deterioration of arterial oxygenation. Most COPD patients develop auto-PEEP during OLV, leading to hyperinflation and increased shunt. However, patients with normal lung parenchyma or those with restrictive lung diseases tend to fall below their FRC at end-expiration during OLV and benefit from external PEEP. Avoiding atelectasis is important in avoiding setting up a pre-inflammatory state leading to injury in both the atelectatic lung and the ventilated portions of the lung which become hyper-inflated. Just as in two-lung ventilation, high tidal volumes in OLV cause or contribute to ALI. In a rabbit model of OLV during isolated perfusion, large tidal-volume (8ml.kg⁻¹) ventilation produced a picture of ALI absent in animals randomized to a lung-protective ventilation pattern (4ml.kg⁻¹ plus PEEP). Large pulmonary resections (pneumonectomy or bilobectomy) should be considered to be associated with some degree of ALI. 42% of pneumonectomy patients who had been ventilated with peak airway pressures > 40cm H₂O had ALI diagnosed radiographically. A retrospective study found that post-pneumonectomy respiratory failure was associated with the use of higher intra-operative tidal volumes (8.3ml.kg⁻¹ vs. 6.7ml.kg⁻¹ in those patients who did not develop respiratory failure). Thus our current understanding of post-thoracotomy ALI supports applying the management strategies of least injurious lung ventilation: FiO₂ as low as acceptable, variable tidal volumes, beginning inspiration at FRC and avoiding atelectasis with frequent recruitment manoeuvres. An observational study in patients undergoing lung cancer surgery by Licker and workers would seem to confirm this. Using a protective lung ventilation strategy (Vt < 8ml.kg⁻¹ predicted body weight, pressure control ventilation, Peak inspiratory pressures < 35cm H₂O, external PEEP 4-10cm and frequent recruitment manoeuvres) in a protocol group (558 patients) vs. conventional ventilation in an historical group (533 patients). They showed a decreased incidence of ALI (3.7% to 0.9%, p < 0.01), atelectasis (8.8 to 5.0, p = 0.018), fewer ICU admissions (2.5% vs. 9.4% p < 0.001) and shorter hospital stay.

Hypercarbia resulting from smaller minute volumes should be tolerated. Permissive hypercapnia has become a central component of protective ventilatory strategies and humans have been shown to be remarkably tolerant of even extreme hypercarbia. Minimizing pulmonary capillary pressure by avoiding over-hydration for patients undergoing pneumonectomy is reasonable while acknowledging that not all peri-operative increases in pulmonary artery pressures are due to intravascular volume replacement. Finally it must be appreciated that not all hyper-inflation of the residual lung occurs in the operating room. The use of a balanced chest drainage system following pneumonectomy to keep the mediastinum in neutral position and avoid hyperinflation of the residual lung has been suggested to contribute to a decrease in ALI in some centres.

ROLE OF VOLATILE ANESTHETIC AGENTS IN LUNG PROTECTION

Volatile agents have immune-modulatory effects. Much work has been done, especially in the cardiac setting, on the role of volatiles in Ischemia-Reperfusion Injury (IRI) and in pre- and post-conditioning. Recent studies in models of ALI, during OLV and in cases of lung ischemia-reperfusion suggest that volatiles may act as pre- and post-conditioning agents inducing...
lung protection by inhibition of the expression of pro-inflammatory mediators. Isoflurane pre-treatment in an endotoxin mediated animal model of lung injury exerted protective effects, as evidenced by reduction of polymorphonuclear recruitment and microvascular protein leakage. Post-conditioning with sevoflurane attenuated lung damage and preserved lung function in an in vivo rat ALI model. Looking at inflammatory markers in the non-ventilated lung, they showed an attenuated inflammatory reaction. Significantly, the sevoflurane group had an improved outcome and significantly lower overall number of adverse events. A study comparing OLV (Vt 10ml.kg⁻¹) with desflurane vs. propofol anaesthesia looked at the inflammatory response in the ventilated lung. The inflammatory markers IL-8, IL-10, PMN elastase and TNF were significantly lower in the desflurane group. Sevoflurane has been shown to be lung protective in a pig lung autotransplant model. While much work remains to be done, this exciting work does point towards a role for volatiles in attenuating the pro-inflammatory response in the lungs to a host of insults, whether this is pre, during or post insult.

TRANSFUSION RELATED LUNG INJURY (TRALI)

Transfusion related acute lung injury has emerged as a leading cause of transfusion morbidity and mortality, with a disproportionate number of cases occurring in the peri-operative period. Anaesthesiologists are routinely involved in transfusion decisions and are well placed to both decrease the incidence, and the morbidity and mortality of TRALI. Diagnostic criteria consist of hypoxia or bilateral pulmonary oedema during or within 6 hours of transfusion, in the absence of circulatory overload. Differences lie in patients with other risk factors for ALI, pre-existing ALI and subtle cases that may not meet current criteria. The exact pathogenesis is not completely understood. While an immune antibody-mediated mechanism is implicated in most cases (with good supporting experimental and clinical evidence), supporting antibodies are not found in 15% or more of cases. Thus an antibody independent “two-hit” model has been proposed. The antibody-mediated mechanism is primarily due to leukoagglutinating antibodies in the transfused plasma binding to recipient neutrophils. These antibody bound neutrophils are activated and sequestered in the lung, where complement activation and release of neutrophil bioactive products results in endothelial damage, capillary leak and ALI. Antibodies implicated are human leukocyte antigens class I and II, and neutrophil-specific antibodies. The two-hit model postulates that an initial insult (e.g. sepsis, surgery, trauma) to the vascular endothelium results in endothelial activation resulting in release of cytokines and adhesion molecules. Neutrophils are then attracted, primed and sequestered in the lung in this pro-inflammatory milieu. A second hit, by transfusion of biologic response modifiers, activates these sequestered neutrophils resulting in the release of oxidases and proteases, resulting in endothelial damage and subsequent ALI. Both mechanisms have their limitations, but it seems reasonable that both may occur and that TRALI may represent the final common pathway of neutrophil activation and subsequent endothelial injury. True incidence is unknown due to the fact that standardized definitions have only recently been developed, but a prospective cohort study looking at an ICU population using current definitions reported an 8% incidence (901 patients), with plasma and platelets having the highest associations. Mortality is estimated at 5-10%. All blood products have been implicated, with most of the products containing more than 50mls of plasma. Data suggest plasma and apheresis platelets have the highest component risk.

Strategies for prevention for transfusion services include, but are not limited to: fresher products, washed components and plasma primarily or exclusively from male donors (avoiding multiparous females). More importantly for the anaesthesiologist is the appropriate use of blood products and to avoid further lung injury. Transfusion triggers must be individualized for each patient and aimed at clinical endpoints. Prothrombin complex concentrates may have a future role in place of FFP and there is certainly a sound theoretical basis for this.

CARDIO-PULMONARY BYPASS (CPB)

Pulmonary dysfunction post CPB is a well described but poorly understood phenomenon. While the incidence of ARDS post CPB is low (<2%) the mortality associated with it is high (>50%). While the Systemic Inflammatory response syndrome initiated by CPB plays a major role, the pulmonary insult is multi-factorial and not all related to the bypass itself. Extra-CPB factors are general anaesthesia, sternotomy and breaching of the pleura. Intra-CPB factors include, but are not limited to hypothermia, blood contact and artificial surfaces, ischemia reperfusion injury, administration of blood products and ventilatory arrest. It must be emphasized that the above strategies, while having good theoretical basis, have showed inconsistent results in the literature in terms of improving pulmonary outcome. Protective post-operative ventilatory strategies of these “at risk” lungs is not clear. A randomized-control trial compared the use of non-protective high tidal volumes (10-12 ml.kg⁻¹) plus low PEEP (2-3 cm H₂O) vs. lung protective low tidal volumes (8 ml.kg⁻¹) plus high PEEP (10 cm H₂O) in patients ventilated for 6h following cardiopulmonary bypass for coronary artery bypass surgery. Serum and bronchial lavage levels of the inflammatory cytokines IL-6 and IL-8 were significantly increased at 6h only in the non-protective ventilation group.

ULTRA-PROTECTIVE LUNG VENTILATION

Following along the continuum of lung protective ventilation in ALI/ARDS is the concept of ultra-
Aerosolized activated protein C in a sheep model of ALI
independent of its effects on body temperature. Inhibition of inflammatory and apoptotic responses, shows beneficial effects in a model of VILI via the attenuation of lung neutrophil recruitment, pulmonary and free radical injury. As compared with conventional ECMO, the Novalung® is a simple, pumpless portable device. Anti-coagulation requirements are much reduced with an aPPT target of 55s. Bleeding complications and blood product requirements are significantly less.

ARDsnet and animal data demonstrates that lower tidal volumes (3ml.kg⁻¹) compared with 6-12ml.kg⁻¹ significantly reduces endothelial and epithelial injury. In other words “protective” tidal volumes can still induce VILI. However clearance of CO₂ and oxygenation become an issue at these lower minute volumes. The Novalung® allows for this marked reduction in MV and the simultaneous correction of PaCO₂ and pH. An animal model of post-pneumonectomy ARDS using the Novalung® and tidal volumes of 2.2mls.kg⁻¹ and respiratory rate of 6 showed significantly better outcomes compared with conventional lung protective strategies. Numerous case reports in humans in a variety of clinical scenarios have been encouraging. Tidal volumes ≤3ml.kg⁻¹, low inspiratory plateau pressure, high PEEP and low respiratory rates are all possible with the Novalung® in situ, causing less VILI and subsequent remote secondary organ failure. While by no means standard of care at this time, this technique represents an exciting area for further clinical research, with significant benefits for patients with respiratory failure refractory to conventional therapy and potential application for use as part of an ultra-protective lung protection strategy.

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 VT. Hypercapnic Acidosis (HCA) 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. 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. Inhaled aerosolized activated protein C in a sheep model of ALI demonstrated improved oxygenation as well as lung aeration (as assessed by CT scan). β-adrenergic agonists have potential benefits by increasing the rate of alveolar fluid clearance by increasing cellular cAMP and have anti-inflammatory properties. A randomized-control trial in 40 patients with ALI showed a decrease in extra-vascular lung water and plateau airway pressure with intravenous salbutamol, although it showed no differences in outcome. Randomized placebo-controlled trial of several different therapies including surfactant, prone positioning, inhaled nitric oxide and anti-inflammatories have not shown significant clinical benefits in patients with established ALI. 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) Non-physiological ventilation in healthy lungs induces ALI.
2) Protective lung ventilation in patients with ALI/ARDS improves outcome.
3) Protective lung ventilation in non-injured 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.

Anesthesiologists manage a heterogeneous group of patients in the peri-operative period; from patients with healthy lungs, patients with “at risk” lungs through to patients with established ALI/ARDS. More patients are at risk for ALI during surgery than previously thought. Appropriate peri-operative management may prevent or ameliorate this lung injury. Although lacking evidence from randomized controlled trials, applying protective ventilatory strategies seems reasonable based on our current understanding of mechanical ventilation and lung injury.

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**INTRODUCTION**

Obesity is defined as a Body Mass Index (BMI) > 30 kg/m²; morbid obesity defined as > 35 kg/m²; super morbid obesity > 50 kg/m² and ultra-obesity > 70 kg/m². As per WHO statistics,1 overweight and obesity are the fifth leading risk for global deaths with one in ten of the world’s adult population being obese. Morbidly obese patients have significant comorbid condition 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 like alteration in pulmonary function, obstructive sleep apnea and difficult airway challenge the anesthesiologist more than the metabolic problems like hypertension, dyslipidemia and insulin resistance.2 Both these factors increase the morbidity during the intra-operative and post-operative 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 anesthetised, paralyzed subjects.3 Regarding lung volumes, there is a reduction in FRC due to the mass load of adipose tissue around the rib cage, 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 FEV1 and FVC. But the ratio of FEV1 to FVC is preserved. CO 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 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 is either depressed or inappropriately suppressed.4,5

**CARDIOVASCULAR CHANGES:**

Obesity is independently associated with left ventricular hypertrophy, characterized by 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 blood pressure. In general obesity leads to hypertension, the probable mechanism is activation of the renin-angiotensin system may occur directly via signals from adipose tissue.6

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 X-ray, pulmonary function tests, non-invasive 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,7 basic screening tests are imperative to identify the additional risk factors.8 Further preoperative testing should be individualized based on co-morbid conditions. Since nearly 70% of morbidly obese patients are prone to have OSA,9 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-
Obese patients have faster gastric emptying time, a large gastric volume and a high incidence of gastroesophageal reflux disease making them prone to aspiration. This risk increases further after post bariatric surgery. Also, obese patients are at significant risk of venous and pulmonary thromboembolism and therefore mechanical and pharmacological method 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. Operating table, trolley, bed and specific equipments like 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 the emergency surgeries.

**INTRAOPERATIVE MANAGEMENT**

**Airway management** – Weight or BMI is just one of several factors to consider during an airway evaluation. A neck circumference greater than 43 cm is associated with an increased risk of difficult intubation. It is imperative to know the severity of OSA to predict the difficulty in mask ventilation and intubation. According to Brodsky et al., patients with a BMI > 35 kg/m² have a six-fold higher risk for difficult laryngoscopy. However, Mashour et al. 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, oxygen saturation following preoxygenation falls more rapidly during apnoea than in those with normal BMI. This effect can be limited by a 25 degree head-up position during preoxygenation. The combination of preoxygenation with reverse Trendelenberg position and nasopharyngeal oxygen insufflation, positive end-expiratory pressure (PEEP) of 10 cm H₂O and noninvasive bi-level positive airway pressure.快速 sequence induction remains essential in the morbidly obese patients with gastro-esophageal 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 the morbidly obese patients with a difficult airway.

**PHARMACODYNAMIC & PHARMACOKINETICS OF ANESTHETICS**

Physiologic changes in obesity affect distribution, protein binding and elimination of the various anesthetic agents. Obese patients have a smaller than normal fraction of total body water, increased blood volume, cardiac output and greater 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 (Vd) based on the total body weight and hydrophilic drugs (muscle relaxant) dosing is based on the lean body weight. A recent study on rocuronium confirmed that the dose should be calculated based...
on the 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 the total body weight.

The volume of distribution (Vd) 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 the total body weight was the major determinant of clearance. Benzodiazepines are highly lipophilic drug. The single intravenous dose is based on the 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**

Following induction of anesthesia, atelectasis increases from 1 to 11% of total lung volume in the morbidly obese patients. Recruitment maneuvers (PEEP & Valsalva) can counteract these effects. The decrease in the compliance of the respiratory system and PaO$_2$ was significantly reversed 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 in unloading of abdominal viscera and reduces pressure on the diaphragm, which improves the FRC. Lateral position is also relatively well tolerated. Trendelenburg position decreases total compliance and FRC, which leads to increased atelectasis and hypoxemia. Obese patients that are breathing spontaneously do not tolerate the Trendelenburg position. Their airway should be intubated and ventilation controlled or assisted. In supine position an increase in BMI proportionally decreases the FRC, pulmonary compliance and increases the ventilation/perfusion (V/Q) mismatch. These effects are significantly reversed by reverse Trendelenburg position. The lithotomy position increases intra-abdominal 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 post-operative pulmonary complications. But the evidences are limited in this issue. In the presence of pneumoperitonium, 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 (10ml/kg/hr) fluid therapy versus low volume (4ml/kg/hr) therapy in laparoscopic bariatric surgery patients and it did not find any significant difference between these two groups in post-operative renal function. Both the groups had intra-operative oliguria, which was unresponsive to fluid administration.

**LAPAROSCOPIC SURGERY**

Morbidly obese patients have markedly reduced supine functional residual capacity, with further decrease in the Trendelenburg position and insufflation of the abdomen with CO$_2$. Morbid obesity and pneumoperitoneum have significant effects on respiratory mechanics, whereas PaO$_2$ was adversely affected only by increased body weight. Repositioning the patient from the supine position into the Trendelenburg or reverse Trendelenburg position had no effect on PaO$_2$ either before or after abdominal insufflation. In non obese patients the difference in PaCO$_2$/ETCO$_2$ was high with large tidal volumes (800ml), but in morbidly obese patients this difference was high with small tidal volumes. The endotracheal tube moves down more 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 based. One lung ventilation is technically possible in the lateral position, since abdominal content falls away from the body and unloads the dependent diaphragm. A large tidal volume ventilation, intermittent alveolar recruitment, continuous positive airway pressure to the collapsed lung and positive end-expiratory pressure (PEEP) to the ventilated lung could help to avoid the hypoxia during one lung ventilation. In general morbidly obese patients are prone for post-operative pulmonary complication and it could be more with thoracic surgery.

**REGIONAL ANESTHESIA**

Regional anesthesia offers distinct advantages, which allows minimal airway manipulation, avoidance
of anesthetic drugs with cardiopulmonary depression, reduced post-operative nausea and vomiting and reduced perioperative opioid requirements. However, the rate of block failure increased incrementally with a higher BMI. Using ultrasound-guided regional anesthesia for peripheral nerve blocks in the obese population led to improved success rates. Epidural analgesia should be considered in obese patients undergoing laparotomy to improve postoperative spirometry. Since 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 require less local anesthetic in their epidural and subarachnoid spaces in order to achieve the same level of block when compared with non-obese controls. However, a recent study showed no difference in spinal bupivacaine requirement between obese and non-obese parturient.

AMBULATORY ANESTHESIA
At one time, patients with BMI > 30 kg/m² or more was considered unsuitable for ambulatory anesthesia. Currently more importance is given to the comorbid conditions than the BMI alone. The ASA guideline has given risk assessment for patients with OSA to undergo 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. ASA recommended that patients with a score above five should not be considered candidates for ambulatory surgery. It may not be safe to undergo patients with severe OSA requiring postoperative narcotic as ambulatory surgical patients. A recent review recommends that the majority of OSA patients may be done as ambulatory surgical patients with few adverse events.

POST-ANESTHESIA CARE
Whenever possible, patients should be extubated wide-awake in the sitting position and transferred to an appropriate postoperative environment. Morbidly obese patients are prone to have postoperative hypoxemia due to atelectasis. Though intraoperative lung recruitment maneuver are important to avoid hypoxemia, CPAP in the PACU helps to improve the oxygenation. Patients with OSA should be instructed to bring their CPAP or non-invasive positive pressure ventilation equipment to the hospital. It has been shown that the postoperative lung functions of bariatric surgery patients are better with Boussingnac CPAP application on extubation rather than in the postanesthetic care unit. Compared with the venturi mask, the Boussingnac CPAP mask improves the postoperative PaO2/FIO2 ratio in morbidly obese patients. The ASA guideline has recommended an extended stay in PACU for obese patients with OSA and monitoring.

POST-OPERATIVE 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 PCA 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 parameters with 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. The combinations of acetaminophen and NSAIDs are superior to the respective single therapy. However, the use of non-selective NSAID in bariatric surgeries should possibly be avoided because of a higher risk for gastric perforation. Though the evidences are limited in the usage of adjuvants like ketamine, lidocaine, clonidine, dexmedetomidine and gabapentin in obese population, it could be a viable option to reduce the perioperative opioid consumption. As per ASA guideline neuraxial opioids and the continuous setting during patient-controlled opioid analgesia is best avoided in obese patients with OSA.

CONCLUSION
Morbidly obese are a special group of patients, they need an extra care during the perioperative period. Understanding the anatomical, physiological, metabolic and pharmacological changes are imperative for the anesthesiologist to modulate the anesthetic technique for better outcomes. Advancement in anesthesia technology like video laryngoscopes, ultrasound and ventilatory modes in anesthesia workstations has made dramatic improvement in the peri-operative 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 these morbidly obese patients could optimise the peri-operative management. Further evidences are required in fluid administration, one lung ventilation and post-operative pain management in morbidly obese patients.

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Reading Your Mind: Monitoring the Brain Under Anesthesia

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“Notwithstanding weaknesses of current devices, a window into the anesthetized brain, albeit a foggy one, may still be useful, in conjunction with information from other monitors, as a generic, all-purpose index of the brain’s response to powerfully sedating drugs.” - Gregory Crosby

ELECTROENCEPHALOGRAPHY (EEG)

As early as 1937, Gibbs, Gibbs and Lennox proposed, “The anesthetist and surgeon could have before them on tape or screen a continuous record of the electric activity of both heart and brain.” Heuristically, this notion is compelling for several reasons. Although the brain is a primary target organ of general anesthesia, the field has not established a standard monitor for the brain. The EEG provides useful information during anesthesia, including surrogacy of unawareness. Today, EEG plug and play modules are available for most intraoperative monitors.

The EEG measures spontaneous electrical activity from neurons near the surface of the cortex. The EEG has excellent temporal resolution, but poor spatial resolution. The EEG montage refers to where the electrodes are placed. A standard EEG has 20 electrodes and 10 channels (10/20 system). With a bipolar montage, there are two electrodes per channel, with one of the two electrodes serving as a reference electrode in relation to the other. With a referential montage, there is a common reference electrode for all the channels. Electrodes are labeled according to their anatomical placement (e.g., frontal pole, frontal, central, parietal, temporal and occipital) and according to laterality (even numbers are right sided and odd numbers are left sided).

The EEG has a complex waveform that is typically far less organized and regular than the ECG waveform. The EEG waveform is made up of several waves, and can be broken down into the component waves through Fourier analysis. Typically all the component waves contribute to the overall waveform, but different waves predominate during different states (e.g., wakefulness, relaxation, REM sleep, non-REM sleep, sedation, general anesthesia, coma). The higher frequency waves (gamma [>30 Hz.] and beta [12-30 Hz.]) have relatively low amplitude and are arrhythmic. These waves are more prominent during wakefulness. With sleep, sedation and general anesthesia, the slower waves (alpha [8-12 Hz.], theta [4-8 Hz.] and delta [0-4 Hz.]) become more prominent. With deeper anesthesia and coma, burst suppression can occur (a suppressed EEG with sporadic burst of EEG activity). An introduction the EEG, including video clips, can be found on the website www.icetap.org (International Consortium for Electroencephalography Training of Anesthesia Practitioners).

Full montage EEG is generally not practical in the operating room. Anesthesia practitioners have typically used limited frontal montages (on the forehead) with one or two channels (e.g., FP1 to F7 and FP2 to F2). Despite the limitations of single area EEG monitoring, frontal montages are useful for anesthesia practitioners in that they display beta waves prominently during wakefulness, and delta waves prominently during general anesthesia (and sleep). An EEG pattern showing an underlying delta rhythm with spindles of concurrent waves at 7-14 Hz. might be reflective of hyperpolarization of the cortex and thalamus, which implies that the cortex could be disconnected from the environment (i.e., external sensory signals are blocked) and noxious stimuli might not be transmitted centrally. Recent research has shown that with relatively brief, structured training, anesthesiologists can learn to recognize important EEG patterns that occur during wakefulness and anesthesia. Recent review articles provide useful introductions to interpretation of frontal EEG waveforms in the operating room and the intensive care unit.

PROCESSED ELECTROENCEPHALOGRAPHY AND AWARENESS

A practitioner cannot spend all her time scrutinizing a complex EEG trace and most anesthesia practitioners have not received formal instruction in EEG interpretation. The introduction of processed EEG devices that displayed a scaled index from 100 to 0 to reflect anesthetic depth was therefore appealing and enjoyed widespread and perhaps uncritical adoption among practitioners. With limited evidence of clinical utility, processed EEG devices garnered FDA approval, which legitimized their use in clinical practice.

A penetrating question that many asked was whether the use of processed EEG devices during general anesthesia would prevent unintended intraoperative awareness. An important observational study suggested that routine processed EEG monitoring might be associated with a dramatic 82% reduction in awareness, but, as an observational cohort study, the results had to be interpreted with caution. The B-Aware investigators argued that in order to adopt processed EEG devices in routine anesthesia practice, convincing proof of efficacy was necessary. They suggested that short of yielding a 0.9% reduction (minimum clinically important effect) in awareness in high-risk (for awareness) patients, such devices could not be recommended for routine use. The B-Aware trial randomized 2,500 patients to a protocol based on a currently used processed EEG monitoring
or to routine clinical practice. The processed EEG protocol was associated with a 0.74% (95% CI, 0.14% to 1.4%) reduction in awareness. Thus the B-Aware trial did not demonstrate a reduction commensurate with the pre-specified minimum clinically important effect. Furthermore, it was difficult to know whether the reduction in awareness was attributable to the monitor or to a protocol that increased clinical vigilance in the experimental group. Finally, about half the patients in the B-Aware trial received total intravenous anesthesia, which is associated with a higher risk for intraoperative awareness.

The B-Unaware and the BAG-RECALL clinical trials enlarged on the results of previous studies. The single center 2,000 patient B-Unaware trial tested a protocol based on a currently used processed EEG device against a protocol based on end tidal anesthetic concentration (ETAC). There was no difference in the incidence of definite awareness between the protocols (0%; 95% CI, -0.56% to 0.57%). Similar to the B-Aware trial, the B-Unaware trial was imprecise (i.e., had wide confidence intervals around the point estimate), which meant that it could rule out potentially clinically relevant benefit (in terms of awareness) of either protocol. However, the results of the B-Unaware trial did suggest that compared with a protocol based on ETAC, a protocol based on processed EEG would not decrease awareness by the minimum clinically important effect pre-specified by the B-Aware investigators. Interestingly, the B-Unaware trial was heavily criticized for its imprecision, whereas the B-Aware trial, which was similarly imprecise, did not face similar censure. This is probably because the B-Unaware trial was a “negative” trial, while the B-Aware trial was a “positive” study. In the B-Unaware trial fewer patients had possible awareness in the ETAC group than in the processed EEG group.

The 6,000 patient, multi-center BAG-RECALL trial was methodologically similar to the B-Unaware trial. This follow-up study showed convincingly that for patients at high risk for awareness, a protocol based on a currently used processed EEG device was not superior to a protocol based on ETAC. Interestingly, and contrary to the hypothesis of the trial, there was a higher incidence of definite awareness, possible awareness and traumatic awareness among patients who were randomized to the processed EEG group.

To help complete the picture somewhat, a recent multi-center study from China showed that for patients receiving total intravenous anesthesia, a protocol based on processed EEG was associated with a dramatic decrease in the incidence of awareness. However, similar to the B-Aware trial, it is unclear how much of the benefit in this trial was attributable to the monitor, and how much to a protocol designed to increased clinical vigilance. Taking all the studies together, it is likely that a protocol based on processed EEG is effective in reducing awareness, especially compared with routine care and in patients receiving total intravenous anesthesia. On the other hand, a processed EEG based protocol is not superior to a protocol based on ETAC in preventing intraoperative awareness.

LIMITATIONS OF EEG AND PROCESSED EEG

There are several possible explanations for the lack of an advantage of a processed EEG based protocol over an ETAC based protocol. Conceptually, it is not clear that anesthesia deepens smoothly or linearly, in which case “depth of anesthesia” might be a problematic concept. In a recent study, Whitlock and colleagues showed that the processed EEG index does not always change predictably with changes in ETAC. This could mean that titrating volatile anesthetic administration according to currently used processed EEG indices might be inappropriate. Other potential reasons why a protocol based on currently available processed EEG devices might be imperfect in preventing awareness include:

- Current devices are not designed based on neurobiological principles of anesthesia or unconsciousness.
- Awareness can occur when processed EEG indices suggest that patients are unaware.
- There is lack of intra-patient reproducibility in currently used processed EEG indices, which brings into question their reliability.
- There is lack of inter-patient reproducibility in currently used processed EEG indices, which also brings into question their reliability. For example young people and older people can have shifts in levels of consciousness at very different values of the processed EEG indices.
- Ketamine and NMDA antagonists (e.g., nitrous oxide) do not produce the typical EEG changes that are seen during general anesthesia.
- As single or dual channel devices, limited montage EEG and currently available processed EEG monitors are unable to assess relational assessments among brain regions (e.g., by transfer entropy).
- State transitions occur rapidly; however, currently used processed EEG devices have a median delay of about 1 minute before they reflect state shifts (e.g., unaware to wakeful).
- Currently available monitors are not specific for anesthesia (e.g., they cannot distinguish general anesthesia from sleep). As such they cannot predict whether a patient will respond to a particular stimulus.
- Electromyography and other artifacts contaminate the EEG trace and might confound clinical interpretation.

IMPROVING OTHER OUTCOMES WITH PROCESSED EEG MONITORING

“An ETAC protocol may inadvertently result in overdosing of the brain in cognitively vulnerable persons. This is worrisome because deep sedation is associated with a higher incidence of postoperative delirium, other adverse cognitive outcomes, and increased mortality in elderly surgical and critically ill patients.” - Gregory Crosby.
It has been suggested that use of a processed EEG index to guide anesthetic administration decreases anesthetic administration and improves patient outcomes, compared with an ETAC guided approach. There are three assumptions underpinning this perspective. First, that an ETAC protocol results in increased anesthetic administration in real world clinical practice. Second, than an ETAC protocol results in worse patient outcomes in real world clinical practice. Third, an increased anesthetic dose within a clinically relevant range results in worse patient outcomes. Recent evidence from large clinical trials does not support any of these three assumptions. In the B-Aware, B-Unaware and BAG-RECALL trials, there was no real difference in anesthetic administration when a processed EEG guided practice. This is unsurprising considering the recent study by Whitlock et al., which showed that, during anesthetic maintenance, a processed EEG index is frequently invariant over a clinically relevant range of volatile anesthetic concentrations. Other investigators have demonstrated this invariance for both volatile anesthetic agents and for propofol. Large clinical trials have also not demonstrated clinically relevant outcomes benefits with processed EEG based protocols. Although one study did show that patients who received general anesthesia had a higher delirium incidence than patients who were sedated, two targeted studies have not shown that a processed EEG monitor decreases postoperative (early) cognitive decline following general anesthesia. There is no compelling evidence that a slight increase in anesthetic dose (e.g., 0.9 MAC rather than 0.6 MAC) during a short anesthetic worsens patient’s outcomes. Data from the B-Unaware trial suggests that patients who received higher anesthetic concentrations did not have worse postoperative complications or outcomes.

GOING FORWARD WITH EEG MONITORING

Clearly there is a long way to go with brain monitoring in the operating room and in the intensive care unit. But EEG has become much more popular among anesthesiology practitioners in recent years and might become a standard monitor in future. All anesthesia practitioners should seek to increase their knowledge of EEG, and should exploit existing educational resources, such as www.icetap.org. It is important that future candidate depth of anesthesia monitors should be conceived according to neurobiological principles and theories of anesthetic-induced unconsciousness. The algorithms defining the monitors should be open source, allowing clinician scientists to evaluate and improve them. Many of the limitations of current devices (e.g., significant delays in response to state changes) can easily be addressed in the new generation of brain monitors.

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Anesthesiology and Cardiac Electrophysiology Practice

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Advances in practice of clinical cardiac electrophysiology (EP) began in the late 1960s with the creation and expansion of EP laboratories. Initially, the primary purpose of these labs was to serve as diagnostic centers for understanding cardiac conduction defects. The success of the EP labs spread into diagnostic studies of patients with tachyarrhythmias, both supraventricular and ventricular. The clinical EP field has now evolved into one where therapeutic techniques have displaced diagnosis as the prime focus. Therapies provided by electrophysiologists encompass two major modalities: 1) catheter-based approaches, for cure or palliation of tachyarrhythmias; and 2) device-based, for both bradyarrhythmias as well as tachyarrhythmias. More recently, EP has influenced the treatment of patients with heart failure, using unique pacing modalities such as CRT. Procedures and interventions in the cardiac EP labs are complex and involve acutely ill patients. As cardiac electrophysiologists gain experience in diagnosing and managing more seriously compromised patients, anesthesiologists are being asked for assistance more frequently. Developing a robust understanding of principles of cardiac electrophysiology and mechanisms of arrhythmias, how the anesthesiology drugs, autonomic tone and physiologic variables affect cardiac EP, and specific issues relating to the complex EP procedures, will aid the anesthesiologist in choosing the appropriate anesthetic techniques for complex EP procedures.

ARRHYTHMIA MECHANISMS

The primary mechanisms of arrhythmogenesis, in order of frequency and importance, are: Reentry, Abnormal automaticity and Triggered activity. Reentry mechanisms are established if circuit pathways are established between connected tissues where different regions of the myocardium have different conduction velocities and refractory times. Circuit pathways can be anatomical pathways such as those seen in WPW, or microcircuits created as a result of dynamic dispersion of refractoriness seen in the setting of AF/VT/VF. Less commonly seen, abnormal automaticity, leads to arrhythmias due to repetitive discharge from a single or few unique foci. Metabolic derangements are a cause of enhanced automaticity, and can be affected by anesthesia management and other perioperative factors. Some of these factors include increased sympathetic hyperactivity, hypoxemia, hypercarbia, acute hypokalemia, hypomagnesaeemia, and changes in myocardial wall tension or ischaemia. A third, less well-defined form of arrhythmia pathogenesis is triggered activity. Triggered activity results when oscillations in the membrane potential (Early or Late afterdepolarizations), occur following an action potential and reach threshold, initiating a new depolarization. Many of the metabolic factors affecting altered automaticity are also responsible for triggered activity.

ANESTHETIC AGENTS AND CARDIAC ELECTROPHYSIOLOGY

It is commonly assumed that many drugs administered by anesthesiologists influence cardiac conduction and myocardial refractoriness. However, data on this subject are limited and the exact influences anesthetics have on cardiac EP in the clinical setting are not entirely evident. Inhalational anesthetics, intravenous agents, neuromuscular blockers, opioids and anticholinergics may all interfere with cardiac EP parameters under certain conditions. Mechanisms by which anesthetic drugs influence conduction include direct myocardial effects, neurally mediated changes in autonomic nervous system tone, and indirectly through changes in acid-base or electrolyte changes occurring during spontaneous and controlled ventilation. The ideal anesthetic should not alter intrinsic pacemaker function, impulse propagation, refractoriness or autonomic tone. It should not suppress the ability to identify aberrant pathways during attempts to trigger and simulate the reentrant arrhythmia. Additionally, anesthesia should be quickly reversible allowing rapid emergence in most instances. Most anesthetic agents have not undergone a comprehensive study in the context of clinical EP study or for ablation procedures. Thus, anesthesia drugs and techniques should be chosen by measured extrapolation from animal and laboratory investigations. A large retrospective study patients undergoing open surgical cryoablation of accessory conducting pathways suggested that for majority of these patients a balanced anesthesia technique can provide adequate conditions for identifying aberrant pathways without significantly altering electrophysiology. Several small clinical prospective investigations have tried to address similar questions regarding various anesthetics during interventional EP and ablation procedures. However, detailed evaluations in patients undergoing AF/VT ablation are not available.

Inhalational anesthetics alter cardiac conduction by a variety of mechanisms. All of the commonly used volatile agents enhance automaticity of secondary atrial pacemakers relative to the SA node accounting for the occurrence of ectopic atrial rhythms and wandering atrial pacemakers. Inhalational anesthetics also demonstrate varying effects on the AV node and His-Purkinje system. Most of the volatile anesthetics prolong
the QT interval and cause dose dependent reductions in myocardial contractile force.9 It is noteworthy that many of the laboratory investigation of arrhythmogenicity of inhalational agents have been performed using either ischemic cardiac canine models or examining thresholds to catecholamine induced arrhythmias. Although an increase in heart rate is frequently seen with isoflurane, conduction of impulses through the His-Purkinje system is slowed. AV nodal conduction is however unaffected by isoflurane.11,12 Effects of sevoflurane are similar to isoflurane. Neuromuscular relaxants influence cardiac electrophysiology by various mechanisms and at different levels in the autonomic nervous system. They modulate autonomic tone through ganglionic stimulation or blockade, act directly at sympathetic nerve terminals or, through histamine release causing vasodilatation and reflex tachycardia. The cholinergic properties of the neuromuscular relaxants can lead to varied effects at autonomic ganglia and parasympathetic nerve terminals. For instance, succinyl choline can precipitate both brady- and tachyarrhythmias. Pancuronium is vagolytic at the postganglionic nerve terminal, increasing heart rate. In addition, pancuronium releases norepinephrine at cardiac sympathetic nerve terminals. Vecuronium may be associated with bradycardia, particularly if used in combination with other vagotonic drugs such as the potent opioids.13 Mivacurium and rocuronium are suggested to be mostly free of cardiovascular side effects. Opioids, especially when administered in high doses have a central vagotonic effect with resultant bradycardia.14 They alter cardiac calcium and potassium ion channels to prolong the action potential mimicking anti-arrhythmic activity of class III anti-arrhythmic agents. During opioid-based anesthesia the QT interval is prolonged,15 but it is unclear if these effects are due to direct membrane-specific actions of opioids or via opioid receptors in the heart. Propofol, another widely used intravenous agent can occasionally cause both abnormalities in heart rate response, however, in a randomized clinical study, there was no effect on AV nodal EP properties.16,17 Benzodiazepines produce qualitatively similar effects but vary in their speed of onset and duration of action. All reduce blood pressure by decreasing peripheral vascular resistance leading to reflex tachycardia.

Central neuraxial modulation of autonomic tone has recently been shown to be effective in management of intractable ventricular arrhythmias, and is being increasingly used in many centers. Prior animal experiments have demonstrated that spinal cord stimulation or left stellate ganglionectomy can decrease the sympathetic discharge of the cardiac ganglia and intracardiac nerve plexus, having a favorable response on sympathetically driven VT.18 Recent report on the successful use of selective thoracic epidural sympathectomy for controlling intractable VT,19 in the setting of persistent ICD shocks for VT storm, suggests that anesthesia techniques of neuraxial/stellate ganglion modulation can be effective in managing some patients with VTs. Practice guidelines proposed by ACC/ACC/HRS also support this approach as a alternative therapy in management of intractable VTs.20

In addition to the consideration given to the choice of drugs, the anesthesiologist has to align his technique of sedation or general anesthesia with the needs of the interventional procedures.21,22 Certainly, there are many procedures that can be accomplished with sedation while others necessitate general anesthesia with varying levels of invasive monitoring.23 Another vital area in which anesthesiologist play a key role in management of these procedures is providing diagnostic imaging echocardiography (TEE) for identifying pre-procedure thrombus (and other abnormal findings) or for guiding placement/ navigation of various catheters and sheaths in the heart.

**CATHETER ABLATION OF ARRHYTHMIAS- EP TESTING AND THERAPY**

It is important for the anesthesiologists to be familiar with the key aspects of EP procedures, and recording techniques (and parameters) in order to understand the impact of anesthetics or anesthesia techniques. An EP study is used to assess a wide range of cardiac rhythm abnormalities including assessing the function of the SA node, AV node and His-Purkinje system. For vast majority of rhythm disorders, the EP study is essential for confirming the diagnosis and for testing response to pharmacological therapy. Reentrant arrhythmias can be intentionally triggered, their location mapped and response to therapy evaluated.24 EP data is typically obtained during programmed atrial and ventricular pacing while localized intracardiac electrograms (EGMs) are recorded. By recording from multiple sites in the heart, conduction time between regions of the heart can be measured. Pacing catheters are typically placed in the high right atrium, the right ventricular apex, and adjacent to the His bundle at the level of the tricuspid valve annulus. Localized depolarization of the proximal His bundle is recorded on the His bundle EGM. Location of the AV node is identified electrically by the earliest His bundle deflection. Measurement of the interval from low right atrium to His bundle (A-H interval) allows estimation AV nodal conduction delay. A pacing catheter/electrode inserted into the right ventricle is used for tachycardia stimulation, overdrive pacing or backup ventricular pacing in the event of significant bradycardia during an EP procedure. Incremental pacing and extra stimulus pacing are means of introducing premature impulses and assessing conduction and refractoriness, or for triggering reentrant rhythms. EP mapping of the site of aberrant conduction is achieved by triggering the abnormal rhythms and locating the by precisely following the sequence of impulse propagation.25 In case of catheter ablation, thermal scar lesions in the region of aberrant conduction are typically created by precise delivery of RF energy. Other sources of energy such as focused ultrasound (HIFU) have also been employed. Catheter ablation is successfully used for several indications- supraventricular macro-reentrant
arrhythmias like atrial flutter, WPW, AVNRT; Atrial fibrillation (isolation of pulmonary veins); Ventricular tachycardias (through either endocardial or epicardial approaches; or for therapeutic ablation of AV node.

TECHNICAL ASPECTS

For EP studies and catheter ablations, the patient is positioned supine on procedure table and 12 -lead electrocardiogram (ECG) as well as defibrillator pads are applied. Venous access is achieved with Seldinger technique. The Femoral vein is most commonly used site for venous access, but the subclavian, internal jugular, or brachial approach also may be used. Multiple electrode catheters are then positioned in the heart. Typical catheter positions include the high right atrium to evaluate SA node function and AV conduction, the right ventricular apex to record ventricular activity, across the tricuspid valve to record bundle of His activity and in the coronary sinus to record left atrial activity. Electrode catheters may be place in the left heart via transeptal or retrograde aortic approach. Systemic anticoagulation with heparin is necessary if the left heart is instrumented. Intracardiac recordings and programmed electrical stimulation (PES) are performed via these electrode catheters. After baseline measurements are recorded, pacing is performed. Burst pacing at various fixed cycle lengths as well as PES is administered, sometimes accompanied by a catecholamine infusion. With PES, a number of stimuli at a fixed cycle length are delivered (e.g., eight beats at a rate of 100 beats/min), followed by a premature beat. The premature beat is moved increasingly earlier, until the refractory period of the tissue is reached. Multiple premature stimuli can be introduced. The technique of PES induces supraventricular and ventricular arrhythmias and allows definitive diagnosis of the mechanism.

Cardiac mapping during the EP study identifies the temporal and spatial distributions of electrical potentials generated by myocardium during normal and abnormal rhythms. This process allows description of the spread of activation from its initiation to its completion within a region of interest. Cardiac mapping is useful in identifying site of origin or a critical site of conduction for an arrhythmia at which RF ablation will be targeted. A variety of mapping techniques have been developed to identify the optimal site for ablation.

ANATOMICAL LOCALIZATION

Anatomical approaches to ablation are used when the arrhythmia has a known anatomic course. For example, in typical atrial flutter, a wavefront proceeds through the isthmus of tissue between the tricuspid valve and inferior vena cava. Thus, ablation is directed to deliver a series of RF lesions to create an ablation line at this isthmus. Ablation of AF focuses on the elimination of triggers for AF via electrical isolation of the pulmonary vein ostia from the body of the left atrium, and sometimes also includes additional lesions made in the body of the left atrium to modify the arrhythmia substrate. This approach is sometimes referred to as wide area circumferential ablation (WACA). Advanced imaging techniques like intracardiac echocardiography, electroanatomical mapping, and three-dimensional CT reconstructions are generally used to facilitate AF ablation.

Catheter ablation is performed with RF energy, which is a low voltage high frequency electrical energy (100 kHz to 1.5 MHz) that is delivered from the tip of the catheter to the endocardial surface. RF energy produces controlled focal tissue ablation, compared with the more extensive damage caused by DC ablation. Lesions are typically 7 to 8 mm in diameter and 3 to 5 mm deep. Temperatures greater than 460o C cause permanent tissue damage. Temperatures greater than 900o C cause coagulation of denatured tissue at the catheter tip, which creates a high impedance barrier to further ablation and increases the risk of thromboembolism. Newer ablation catheters with saline irrigation to cool RF catheter tip have been developed to address these problems. Cryothermal ablation has been developed to overcome some of the disadvantages of RF ablation such as tissue disruption by excess heating and the generation of inhomogeneous lesions. Cryoablation produces adherence of the catheter tip to the endocardium, which prevents dislodgement. In addition, reversible cryomapping lesions can be placed prior to creation of permanent lesions. Multiple reports of cryoablation for treatment of AVNRT and AF have reported efficacy and safety similar to that of RF. Other energy sources such as microwave energy and ultrasound energy are still investigational. Epicardial mapping and ablation done via subxyphoid access of the pericardial space have been reported to be successful in variety of arrhythmias, especially VT who had failed endocardial ablation, but it is currently performed at only few centers.

Following successful ablation, repeat programmed electrophysiologic stimulation is performed to make certain that the target arrhythmia is no longer inducible and that no other tachycardias can be provoked. At the conclusion of the procedure, the access sheaths are pulled, and the patient remains at bed rest and is monitored for four to six hours for complications. Depending on the nature of the procedure, the patient may be admitted to the hospital overnight or discharged home the same day.

COMPLICATIONS

Most complications are related to the vascular access (3-4%) and include bleeding, infection, hematoma and vascular injury. Intracardiac catheters and programmed cardiac stimulation can induce hemodynamically unstable arrhythmias that require immediate therapy. Complete heart block requiring permanent pacemaker implantation, and cardiac perforation and tamponade occur in less than 1-2% of patients. Pulmonary vein isolation for AF rarely can lead to pulmonary vein stenosis and atrioesophageal fistula (0.01-0.2%). Other infrequent complications include valvular damage, systemic embolization and stroke (<1%) when working...
within the left heart, phrenic nerve injury, and skin burns from radiation. Death from any of these complications is extremely rare (0.1-0.3%). Structural heart disease and the presence of multiple targets for ablation may increase the likelihood of complications.

ANESTHETIC CONSIDERATIONS

Most catheter ablations for AVNRT, SA nodal and atrial reentrant tachycardia, simple atrial flutter and WPW syndrome can be performed using moderate depths of procedural sedation or deep sedation by infusion of propofol. Complex AF ablation procedures can be prolonged (6-8 hours) and carry the risk of atrioesophageal fistula. Installation of an enteral contrast agent via an orogastric tube placed at the junction of esophagus and stomach can reduce the risk of this complication. General anesthesia with endotracheal intubation should be used to protect the airway when an oral contrast agent is used. Paralytic drugs should be avoided so that phrenic nerve stimulation during pacing can be recognized. General anesthesia should also be used for complex catheter ablation of destabilizing monomorphic VT in patients with ischemic heart disease.

Monitoring electrical and mechanical cardiac activity is crucial in any electrophysiology procedure. Of the standard monitors, continuous ECG and peripheral pulse monitoring are particularly useful. The need for invasive arterial monitoring is typically dictated by the patient’s preoperative condition. Use of a magnetic mapping system (Stereotaxis, St. Louis, MO, USA) mandates the use of MRI compatible anesthesia equipments and monitors. Temperature monitoring is also important for prolonged ablation procedures. Monitoring esophageal temperature while ablating around pulmonary veins for AF has been reported to reduce the risk of atrioesophageal fistula. Surface defibrillation/pacing pads should be placed on all patients, and a functional defibrillator should be readily available. Transesophageal echocardiography is routinely performed to exclude thrombus in the left atrial appendage of patients with AF and atrial flutter. Air bubbles should be excluded from intravenous lines to avoid paradoxical air embolism in patients requiring transeptal puncture. During left heart instrumentation, heparin anticoagulation should be monitored with by activation clotting time (ACT) with target ACT of >300. Intravenous fluid infusion via saline-irrigated tip ablation catheters should be taken into account when calculating total fluid intake. Transseptal catheterization and isoflurane on automaticity and recovery of automaticity from overtdrive suppression in Purkinje fibers derived from canine hearts. Anesthesiology 1991; 75: 96-105.

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The Poor Man’s Epidural: Systemic Local Anesthetics and Surgical Outcomes

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Epidural local anesthetics have several benefits in addition to providing excellent pain relief. For example, they are very effective in shortening the duration of ileus after abdominal surgery. They also effectively decrease the incidence of thrombosis, even in patients already on anticoagulants. The mechanisms behind these effects are not well understood, but it is conceivable that inflammatory modulatory effects of local anesthetics absorbed from the epidural space may contribute to these effects. If so, similar benefits could be obtained by intravenous administration of local anesthetics, and this has indeed been shown to be the case. This is of clinical interest, as many patients can not or will not have epidurals placed, even if they would potentially benefit from their use.

The molecular mechanisms of these actions have not been elucidated, but local anesthetics have well-defined effects on the inflammatory system that might be of relevance. For example, they prevent overactivation of neutrophils without interfering with their normal function (i.e. they block priming without interfering with activation). If this action is relevant, then one would expect intravenous local anesthetics to interfere with excessive physiologic responses to surgery (e.g. thrombosis) without interfering with normal responses (e.g. not inducing bleeding). In addition, if priming of neutrophils can be avoided during the immediate perioperative period, effects would be expected to outlast the duration of the local anesthetic. Such seems indeed to be the case.

The most conclusive data on the benefits of intravenous local anesthetics are on the topics of coagulation, bowel function, and pain, with several meta-analyses now confirming these benefits. For example, intravenous local anesthetics decreased the incidence of deep venous thrombosis after hip replacement (without anticoagulation) from approximately 80% to less than 20%, but without increasing bleeding complications. The ability of intravenous local anesthetics to prevent “windup” of pain responses after repeated stimulation has been well documented in volunteer studies, and in a variety of models: finger web pinch, skin incision, and burns. In these models, pain as well as hyperalgesia were reduced. As anticipated from this ability to reduce pain, intravenous local anesthetics also reduce anesthetic requirements during surgery, by approximately 30%. In clinical trials, intravenous lidocaine has been effective in providing long-lasting pain relief, in particular after abdominal surgery. In prostatectomy, laparoscopic colectomy, other types of abdominal surgery and outpatient surgery, pain and morphine consumption were decreased. Although not all studies found this benefit, a recent meta-analysis confirmed these findings in abdominal surgery.

Duration of ileus is also reduced significantly by intravenous local anesthetics in settings such as prostatectomy and colectomy. Probably as a result of this benefit, length of hospitalization after abdominal surgery has been consistently reduced by approximately 1 day.

Many of these benefits mimic those of epidurals. Indeed, in a direct comparison of epidural bupivacaine and intravenous lidocaine after colectomy, no significant differences were observed between the techniques in pain scores, opiate consumption, duration of ileus, time to oral food intake and time to hospital discharge. But there are differences between the techniques. Importantly, these benefits of intravenous local anesthetics seem to depend on type of surgery, and have not been found after hip replacement or abdominal hysterectomy.

In summary, intravenous local anesthetics can function effectively as a “poor man’s epidural” in patients undergoing abdominal procedures, who can not or will not have an epidural placed.

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What to Do: Controversial Case Studies in Regional Anesthesia

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Which patients with chronic pain present with acute pain issues?
- Chronic nonmalignant pain
  - Back pain and “failed back” syndrome
  - Headaches
  - Diabetic neuropathy
  - Herpes virus-related pain syndromes
  - Sickle cell disease
  - Phantom limb pain
- Complex regional pain syndromes
- Mixed conditions (e.g., neuropathic pain + osteoarthritis)
- Cancer-related pain
- Substance-abusing patients

Management of Acute Pain in the Chronic Pain Patient
Discussion Outline
- Introduction
- Sickle cell disease
- Phantom limb pain
- Substance-abusing patients
- Conclusions

Case 1: Phantom Limb Pain
- 30 year old woman
- Injured right foot 8 months previously
- 2 non-healing fractures of metatarsals
- Alldynia, hair loss, impaired nail growth
- Cannot bear weight since injury
- Scheduled for below-knee amputation
- Consultation from orthopedist for pre-emptive technique to prevent phantom pain

Which patients with chronic pain present with acute pain issues?
Short answer = all of them!
**Case 1: Phantom Limb Pain**

- Lumbar epidural placed 1 day before surgery
- Bupivacaine 0.125% + morphine 0.005% infused 10 ml/hr
- Bupivacaine 0.5% sciatic nerve block, ropivacaine 0.5% femoral nerve block, + epidural infusion for anesthesia
- Ropivacaine 0.2% + clonidine femoral infusion + epidural morphine used for 2 days postoperatively

**Phantom Pain Named**

- S. Weir Mitchell serves as medical officer during American Civil War
- Gunshot Wounds and Other Injuries of Nerves (1872)
  - Causalgia
  - Phantom limb pain
- Never promoted to Professor at either Jefferson Medical College or University of Penn
- Founds American Journal of Physiology

**Case 1: Phantom Limb Pain**

- Patient develops phantom sensations when infusions discontinued

**Phantom Symptoms Frequent in Amputees**

- N=536 (19% upper, 81% lower limb amputees)
- Most have phantom pain (upper extremity 41%; lower extremity 80%)
- Described as shooting, stabbing, burning

**Phantom Pain Described**

- Paré postulates that peripheral factors and central pain memory may cause post-amputation pain (1552)
- Describes phantom pain for first time

**Amputation Leads to Cortical Reorganization**

- Subjects with prior arm amputation (± phantom pain) & normals told to pucker and "unpucker" their lips in time with a metronome
- Shift of mouth to hand representation in primary somatosensory cortex

---

Ambroise Paré 1517-1590

Dijkstra J Pain Symptom Manage 2002;24:578-80
Morgan et al Clin Ortho Rel Res 2002;397:281-4

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Pharmacological Management of Phantom Pain

- COX inhibitors
- Opioids
- β-blockers
- Neuroleptics
- Anticonvulsants

- NMDA receptor antagonists
  - Ketamine
  - Memantine
- Barbiturates
- Muscle relaxants

Psychological Management of Phantom Pain

- Electromagnetic biofeedback
- Temperature biofeedback
- Cognitive-behavior therapy
- Sensory discrimination training
- Hypnosis

Surgical Management of Phantom Pain

- Stump revision
- Neurectomy
- Sympathectomy
- Rhizotomy
- Cordotomy

- Tractotomy
- Dorsal column stimulator
- Deep brain stimulator

Other Techniques for Management of Phantom Pain

- TENS
- Acupuncture
- Physiotherapy
- Ultrasound
- Manipulation
- Prosthesis training & fitting

Anesthetic Management of Phantom Pain

- Nerve blocks
- Epidural techniques
- Sympathetic blocks
- Local anesthesia
- Lidocaine infusion

Evidence for Optimal Treatment of Phantom Limb Pain

- 12 trials with a total of 375 patients identified through Medline
- 3 RCTs and 3 randomized cross-over trials
- 8 trials examined acute treatment (3-epidural, 3-nerve blocks, 1-calcitonin, 1-TENS)
- 4 trials examined postoperative interventions (2-TENS, 1-metal thread sock, 1-ketamine)
Evidence for Optimal Treatment of Phantom Limb Pain

- 3 of 8 acute trials had positive result
- 3 of 4 late trials had positive result
- Inconsistent results with preemptive epidural, early nerve blocks, mechanical vibratory stimulation
- **Conclusion:** “There is currently a gap between research and practice in the area of phantom limb pain.”


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Management of Acute Pain in the Chronic Pain Patient

**Discussion Outline**

- Introduction
- Sickle cell disease
- Phantom limb pain
- Substance-abusing patients
- Conclusions

---

Case 2: Substance Abuse

- Surgery plan: revise previous open reduction + internal fixation, skin grafting
- Thiamine and multivitamins
- Beer supplied 4 times per day
- Infraclavicular brachial plexus catheter placed for surgical anesthesia

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Case 2: Substance Abuse

- 0.2% ropivacaine + clonidine 10 ml/hr infused postoperatively
- Maintenance drugs resumed after surgery
- Weaned from regional analgesia on postoperative day #3
- Discharged home on preoperative regimen

---

Case 2: Substance Abuse

- 48 year old man with severe trauma to left hand 2 months ago
- Now has allodynia, hair loss in the hand
- >30 year history of excessive drinking
- Now admits to 6 cans of beer/day
- Also takes Oxycontin™ 40 mg every 8 hours; oxycodone 10-15 mg every 3-4 hours as needed

---

Prominent Citizens are Subject to Substance Abuse
Inadequate Analgesia is Common
Why?

- Inhibitory influence of medical boards, state and federal regulations
- Lack of knowledge base
- Fear of dependency and addiction
- Cultural and societal barriers to opioid use
- Adherence to bad habits
- Bias regarding different groups

Principles of Pain Management in the Addicted Patient

- Do not discontinue opioids until acute pain is resolved
- Scheduled dose or PCA better than PRN opioids
  - Requests may be viewed as drug seeking
  - Avoid conflict with staff
- Continue maintenance opioids
- Useful adjuncts
  - COX inhibitors
  - Regional analgesia if possible

Chronic pain is Common in Chemical Dependence

- Patients sampled in 2 outpatient methadone maintenance clinics (n=390) and 13 short term residential programs (n=531)
- Frequent incidence of pain in last week (P1W) and chronic severe pain (CSP)

Common Management Errors with Addicted Patients

- Opiates give to NA 6 months into recovery; drug ideation returns; relapses
- Sedatives/anxiolytics given to recovering alcoholic after GI surgery; relapses
- Alcoholic with 10 yrs sobriety receives opioids and diazepam for back pain; relapses; dies of EtOH-related illness within 12 months
- Failure to recognize risks & initiate an intensified program

Anesthesia Management of Addicted Patient

- Infections (HIV, TB, endocarditis, hepatitis)
- ECG abnormalities
- Prophylaxis against withdrawal syndromes
  - Vitamins
  - Alcohol
  - Opiate abusers
  - Methadone
- Enzyme induction vs. liver injury
- Tolerance
- Useful adjuncts
  - Regional anesthesia and analgesia
  - COX inhibitors

Management of Acute Pain in the Chronic Pain Patient

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Management of Acute Pain in the Chronic Pain Patient

Conclusions & Suggestions

- Avoid disrupting chronic regimen
  - Make it easy to identify your changes
  - Use regional analgesia when feasible
  - Make sure patient has follow-up appointment with his personal physician
  - Plan ahead for discontinuation of “new” (acute pain related) medications after the acute episode is over

Some Drugs Have Been Demonized

10, 20, 40, 80 mg Oxycontin™ tablets

Clinical Case 3

Perioperative Nerve Injury

Clinical Scenario

- 68 year-old male
- Left total knee arthroplasty
- Degenerative osteoarthritis
- PMH: s/p Left knee arthroscopy x 2
- Meds: Sulindac 200 mg PO QD
  ASA 81 mg PO QD
  Ibupofen 400 mg PO PRN
- Allergies: NKDA

Clinical Scenario

- Laboratory Evaluation
  - Hgb 14.6
  - Platelet 259
  - Cr 1.3
- ECG: NSR at 63 bpm
  Normal ECG
- Anesthetic Plan: Femoral Catheter
  Sciatic nerve block
  GETA vs. Spinal
# Clinical Scenario

- Laboratory Evaluation
  - Hgb: 14.6
  - Platelet: 259
  - Cr: 1.3
- ECG: NSR at 63 bpm
  - Normal ECG
- Risks of nerve injury?
  - Peripheral nerve blocks?
  - Spinal?

# Rates of PNI vs. PNB

![Graph showing rates of PNI vs. PNB from 1988-02 to 2003-07](image)

# Perioperative Nerve Injury - Mayo Clinic

- Retrospective cohort study (20-year)
- 12,329 patients
- Total knee arthroplasty
- Neurologic complication rate: 0.79% (1:125)
  - All causes of PNI (Surgical, Anesthetic, Medical)
- Risk Factors
  - Age: O.R. 0.68 (per decade)
  - Bilateral procedures: O.R. 2.51
  - Tourniquet time: O.R. 1.28 (per 30-min)

* P < 0.05

---

# Perioperative Nerve Injury - Mayo Clinic

- PNI was *not associated* with type of anesthesia
  - GA vs. Neuraxial (Spinal or Epidural)
- PNI was *not associated* with peripheral nerve blockade
  - Patients with PNI + PNB = Complete recovery less likely

---

# Perioperative Nerve Injury - Mayo Clinic

- PNI was *not associated* with type of anesthesia
  - GA vs. Neuraxial (Spinal or Epidural)
- PNI was *not associated* with peripheral nerve blockade

---

# Table 5: Characteristics and Clinical Course of Perioperative Nerve Injury

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Primary (n = 50)</th>
<th>Unilateral (n = 13)</th>
<th>Bilateral (n = 37)</th>
<th>Overall (n = 87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of peripheral nerve blockade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal</td>
<td>36 (72)</td>
<td>8 (62)</td>
<td>28 (76)</td>
<td>64 (73)</td>
</tr>
<tr>
<td>Neuraxial</td>
<td>4 (8)</td>
<td>0 (0)</td>
<td>4 (11)</td>
<td>8 (9)</td>
</tr>
<tr>
<td>GA</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Nerve conduction</td>
<td>49 (98)</td>
<td>8 (62)</td>
<td>41 (108)</td>
<td>58 (66)</td>
</tr>
<tr>
<td>Neuropathy consultation</td>
<td>14 (28)</td>
<td>2 (15)</td>
<td>12 (32)</td>
<td>28 (32)</td>
</tr>
<tr>
<td>Embolography</td>
<td>14 (28)</td>
<td>2 (15)</td>
<td>12 (32)</td>
<td>28 (32)</td>
</tr>
<tr>
<td>Other</td>
<td>39 (78)</td>
<td>7 (53)</td>
<td>32 (86)</td>
<td>72 (82)</td>
</tr>
<tr>
<td>Complete</td>
<td>50 (100)</td>
<td>13 (100)</td>
<td>37 (100)</td>
<td>87 (100)</td>
</tr>
</tbody>
</table>

Complete Neurologic Recovery:
- 82% (All) vs. 44% (PNI)*)

* P = 0.03
Serious Complications Related to Regional Anesthesia

- Prospective Survey in France
- **Regional Anesthetics:** 103,730
  - Neuraxial 71,053 (68%)
  - Peripheral blockade 21,278 (21%)
  - IV regional anesthesia 11,229 (11%)
- **Complications:**
  - Cardiac arrest
  - Neurologic injury
  - Death
  - Seizure

Incidence of Neurologic Complications

- Prospective randomized studies
- Anesthesia literature
- 2000 – 2010
- Variable neurologic complication rates
- Reported Frequency: 0.02%
- 11%
- +500-fold Difference

Comparing Clinical Studies

*Apples vs. Oranges?*

- Sample sizes
- Surgical procedures and anesthetic techniques
- Providers performing blocks
- Patient status during block placement
- Exclusion criteria
- Definition of Perioperative nerve injury
- Method of postoperative evaluation
- Time of follow-up

Clinical Case 3

*Perioperative Nerve Injury*

- Neurologic Complications: 34 (37%)
- Neuraxial anesthesia: 0.04% (1:2500)
- PNB Injury: 0.02% (1:5000)
**POD 1**

**06:30**
Comfortable without complaint; VAS 0/10
Distal sensorimotor block consistent with PNB’s

**18:30**
Complains of mild-moderate foot edema
Dense distal motor block

**19:10**
Femoral catheter D/C  → Residual sciatic blockade

**10:31**
Severe edema entire lower extremity → Elevate + Ice

**16:45**
POD 3
Pain posterior knee; Significant swelling persists
Distal neurologic deficit remains
Consult RMH Pain Service

**Neurology Consult**

*Postoperative Day 4*

- **L4**
- **SP**
- **T1**

- Joint proprioception (-4)
- Superficial pain (-3)
- Temperature (-3)

Total Tourniquet Time: 1 hour 39 minutes
**Differential Diagnosis**

- Prolonged effect of sciatic nerve block
- Compartment syndrome with ischemia
- Direct sciatic nerve injury
  - Surgical
  - Anesthetic

**Risk Factors for Nerve Injury?**

**Perioperative Nerve Injury**

**Patient Risk Factors**

- Pre-existing neurologic deficits
- Diabetes mellitus
- Age and Gender
  - Upper extremity: Male + older
  - Lower extremity: Female + younger
- Extremes of body habitus
- Tobacco use
- Preoperative valgus deformity or knee contracture

**Risk Factors Associated with Neurologic Injury**

**Perioperative Nerve Injury**

**Surgical Risk Factors**

- Surgical trauma or stretch
- Tourniquet ischemia
- Surgical bleeding
- Perioperative inflammation
- Vascular compromise
- Postoperative edema
- Infection or abscess
- Cast compression
- Patient positioning

**Perioperative Nerve Injury**

**Contributing Factors**

1. Patient Risk Factors
2. Surgical Risk Factors
3. Anesthetic Risk Factors

**Perioperative Nerve Injury**

**Anesthetic Risk Factors**

- Mechanical trauma
  - Needle or catheter
  - Intrafascicular injection
- Chemical injury
  - Local anesthetic neurotoxicity
- Ischemic injury
  - Epiinephrine
  - Perineural edema
Clinical Case 3

Perioperative Nerve Injury

Clinical Scenario

- Severe lancinating pain across the dorsum of foot
- Electrical (shock-like) symptoms on plantar surface
- Pins-and-Needles sensation throughout
- Present everyday
- Variable intensity (VAS 2 to 8)
- Difficulty sleeping secondary to pain
- Minimal relief with gabapentin & nortriptyline

Decline of Sensory and Motor Action Potentials after Axonal Injury

Nerve Conduction Studies

9-weeks postop

...Findings are consistent with a severe, predominantly axonotmesis lesion of the left peroneal nerve distal to the innominate to the short head of the biceps femoris (i.e., distal to the mid-Bogh...
Regional Anesthesia and Perioperative Nerve Injury

The “Double-Crush” Phenomenon

Patients with pre-existing neural compromise may be more susceptible to injury at another site

“Double-Crush Phenomenon”
Multiple Contributing Factors

- Needle trauma
- Painful paresthesias
- Ischemic injury
- Male gender
- Increasing age
- Vascular compromise
- Pre-existing diabetes mellitus
- Surgical trauma or stretch
- Tourniquet ischemia
- Perioperative inflammation

- Catheter trauma
- Local anesthetic toxicity
- Perineural edema
- Extremes of body habitus
- Anatomic abnormalities
- Postoperative infection
- Hematoma
- Cast compression or irritation
- Patients positioning
- Surgical scarring or adhesions

Damage of “dual injury” far exceeds the expected additive damage caused by each isolated insult
“Double-Crush Phenomenon”
Multiple Contributing Factors

- Needle trauma
- Painful paresthesias
- Ischemic injury
- Male gender
- Increasing age
- Vascular compromise
- Pre-existing diabetes mellitus
- Surgical trauma or stretch
- Tourniquet ischemia
- Perioperative inflammation
- Catheter trauma
- Local anesthetic toxicity
- Perineural edema
- Extremes of body habitus
- Anatomic abnormalities
- Postoperative infection
- Hematoma
- Cast compression or irritation
- Patients positioning
- Surgical scarring or adhesions

Anticoagulation in the Perioperative Period
Managing Epidural Blockade

Denise J. Wedel, M.D.
Professor of Anesthesiology
College of Medicine, Mayo Clinic

The ASRA Practice Advisory: Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy (3rd Ed)

www.asra.com
RAPM (35) Jan-Feb 2010 pp64-101

Summary
Perioperative Nerve Injury

1. Neurologic complications are extremely rare (Neuraxial > PNB)
2. Identify potential patient and surgical risk factors pre-operatively
3. Assess R/B/A of regional technique (minimize anesthetic risk factors)
4. Vigilance throughout the entire perioperative period
   • Rapid diagnosis and intervention critical
Why Anticoagulate Patients At All?

- Risk of a first episode of VTE in Caucasians 1-2 per 1000 up to age 40
- Risk doubles each subsequent decade
- Aging and obesity in population will increase risk
  - U.S. - 2 million DVT/yr \(\Rightarrow 600,000\) PE \(\Rightarrow 200,000\) deaths

Better Thromboprophylaxis is the Goal -- Why?!

- Venous Thromboembolism (VTE) has a "high" risk of recurrence
- Inherited risk of a thrombophilic mutation in the Caucasian population ranges from 1-7%
- Half of patients with VTE have no risk factors (idiopathic)

Contraindications to Regional Anesthesia

- Patient refusal
- Local anesthetic allergy
- Ongoing or progressive neurologic disease
- Infection at needle insertion site
- Coagulopathy
- Systemic infection?

Risk of VTE Recurrence

- Highly variable
- Genetic
  - (Homozygous vs. Heterozygous)
  - Specific mutation
    - Factor VIII levels/lupus anticoagulant/antiphospholipid >>
    - Mild hyperhomocysteinemia >
    - Factor V Leiden/prothrombin
Risk of VTE Recurrence

- Half of patients with VTE have no risk factors (idiopathic)
- Cancer
- Transient factors (e.g. surgery) are associated with lower risk of recurrence
- Residual thrombosis on compression ultrasound
- Obstetric complications (antiphospholipid antibody syndrome)

Case 4: Chronic Coumadin Rx Postoperative SQ Heparin

- 60 yo patient for “Stoppa” hernia repair
- BMI 41
- Coumadin for hx DVT 6 years ago
  - INR 1.8 when D/C’ed 7 days ago
  - No INR on within 24h surgery
- Epidural for postop pain management
- TID subcutaneous heparin ordered

Characteristics of an “Ideal” Anticoagulant

- High efficacy-to-safety
- Predictable dose response
- Parenteral and oral administration
- Rapid Onset
- Rapid Offset
- Safe antidote
- No need for laboratory monitoring
- No non-anticoagulant side effects
- Minimal drug interactions
- Reasonable cost

Which Anticoagulants are the Problem?

- ASA and NSAID’s
- Coumadin
- Unfractionated heparin
- LMWH and relatives
- Thrombolytics
  - Combinations of the above
- New “better” thrombolytics

Stoppa Open Hernia Repair

- Anesthetic implications
  - Very large incision with significant postoperative pain
  - Patient frequently has co-morbidities
  - Several hour procedure
  - Minimizing coughing and straining at emergence desirable
Oral Anticoagulation and RA

- Preoperative oral anticoagulation
  - Contraindicated in fully anticoagulated patients
  - Warfarin 5-10 mg preop will not elevate PT
  - Limit epidural analgesia to 2-3 days
  - Monitor PT
  - Evaluate clinically for evidence of cord compression

Vitamin K Dependent Coagulation Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Half-life (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>48 - 120</td>
</tr>
<tr>
<td>VII</td>
<td>2 - 6 *</td>
</tr>
<tr>
<td>IX</td>
<td>18 - 30</td>
</tr>
<tr>
<td>X</td>
<td>24 - 60</td>
</tr>
</tbody>
</table>

* Primary determinant of INR during initiation of therapy

Oral Anticoagulants and Neuraxial Block

Recommendations

- Monitor PT (INR) daily
- Remove catheter when INR < 1.5
- Continue neurologic assessment 24 h after catheter removal
- No definitive recommendation for removal or maintaining a catheter when INR > 3
- Individual factor levels may be helpful


Coumadin and INR Monitoring

- Anticoagulant effect monitored by INR and PT
  - Extremely sensitive to factor VII levels
  - INR prolonged when factor VII activity is 55% of normal
  - 40% factor VII activity with INR of 1.4 (initiation of therapy)
  - Normal INR after discontinuation of warfarin present with only 40% of factor II, IX, and X activity
  - “Safe” INR different for warfarin initiation and discontinuation

Subcutaneous Heparin Pharmacology

- Heparin 5,000 units subcutaneously
  - Peak effect 40-50 min
  - Duration of action 4-6 h
  - Activated partial thromboplastin time (APTT) may remain within normal range
  - Anticoagulant effect monitored by anti-Xa activity or heparin level
Subcutaneous Heparin Pharmacology

- BID subcutaneous heparin
  - 15% of patients have elevated aPTT
  - 2-4% are therapeutically anticoagulated
- “Trough” effect may be important safety feature
  - TID – minimal trough

Subcutaneous Heparin Recommendations

- No apparent increased risk with usual BID doses (5000 U)
- In high risk patients, consider delaying until 1h after needle placement
- aPTT may be helpful
- TID dosing recommendation may increase risk

Subcutaneous Heparin TID Dosing

- TID dosing regimen not shown to be more efficacious than BID with compression devices
- Increase in minor and major hemorrhagic events
- No prospective study showing safety

If there is a catheter, is it epidural or spinal?

LMWH and Regional Anesthesia

- First case of spinal hematoma associated with LMWH reported in 1989
  - Minimal bleeding during epidural catheter placement
  - Irreversible paraplegia 3 hr later (after 3rd LMWH injection)
  - Epidural hematoma T9-L4 evacuated without neurologic improvement

LMWH and Regional Anesthesia

- Enoxaparin (Levenox®) released for use by FDA in May 1993
- Six spinal hematomas associated with neuraxial anesthesia reported to manufacturer
- Risk factors include:
  - Preop or early postop dosing
  - Dose administration
  - Epidural anesthesia/analgesia

Tryba M. Reg Anesth 1989

Rhone-Poulenc Rover Pharmaceuticals, Inc., 1995
**FDA Medwatch Reports**

**LMWH**

- April, 1998: 40 cases of spinal hematoma associated with central neuraxial blockade (additional 20 cases reported after review)
- 26 Continuous Epidural/Spinal
  - 17 had LMWH with catheter indwelling
  - 12 had other antithrombotic meds
  - 15 received initial dose preop (4) or early postop
- 70% elderly female

**LMWH: Pharmacology**

- 90% bioavailability after subcutaneous administration
- Peak anti-Xa activity 3-4 h
- T½ 3-4X unfractionated heparin
- Renal clearance

**LMWH Hematomas**

**Diagnosis**

- Radicular pain uncommon
- New onset numbness/weakness or bladder dysfunction
- Median time from administration of LMWH to neurologic dysfunction - 3d
- <1/3 of patients had good recovery

**LMWH: Risk Factors**

- Increased age
- Female gender
- Spinal stenosis
- Traumatic needle/catheter placement
- Indwelling catheter
- Pre-intra-early postop dosing
- Concomitant antiplatelet
- BID dosing

**Enoxaparin-Related Hematomas**

- Incidence difficult to determine
- Estimated 1:1000-1:10,000 central neuraxial anesthetics
- Technique affects frequency
  - Spinal 1:100,000
  - Continuous epidural 1:3,000

**LMWH: Off Label Use**

- Pregnancy
- “Bridge Therapy” from Coumadin
  - Heart valve
  - Hx PE
- Hypercoagulable individuals
  - Genetic conditions
**LMWH and Neuraxial Block Recommendations**

- Avoid other anticoagulants and antiplatelet agents
- Monitoring of anti-Xa level not recommended
- Preoperative LMWH therapy
  - Delay needle placement 10-12 h after LMWH
  - Longer interval required for high-dose (Enoxaparin 1mg/Kg) applications (at least 24h)

**Case 6: Epidural Catheter Postoperative Disaster**

- Unplanned anticoagulation
  - Thrombolytic treatment
  - Thrombin inhibitors
  - Factor Xa inhibitors

---

**Postoperative LMWH**

- BID dosing
  - Indwelling catheter not recommended
  - Remove catheter at least 2 h prior to first dose
  - Start LMWH 24h after needle placement - adequate hemostasis

---

**Postoperative LMWH**

- Once daily dosing
  - Indwelling catheter can be maintained
  - Start LMWH 6-8 hr after needle placement, 2nd dose no earlier than 24 hr after first
  - Remove catheter 10-12 hr after last dose and wait at least 2 hr to re-dose
  - Avoid any concomitant anticoagulant therapy

---

**Thrombolytic Therapy and Regional Anesthesia**

- Epidural anesthetic for intra-arterial catheter placement in a patient with femoral artery occlusion
  - Atraumatic epidural catheter placement
  - Postop urokinase infusion
  - Back pain 3 h later which progressed to paraplegia
  - Epidural hematoma T12-L4
  - Laminectomy performed, good neurologic recovery

**Horlocker and Wedel, Reg Anesth Pain Med 2010**

**Dickman AC, Anesthesiology 1990**
Fibrinolytic/Thrombolytic Drugs and Neuraxial Block

Recommendations

- Neuraxial block in the presence of fibrinolytic or thrombolytic therapy represents unacceptable risk
- Concomitant heparin therapy
- No recommendations for removal of catheter in patients who unexpectedly received fibrinolytic or thrombolytics
- Measurement of fibrinogen level may be helpful


Psoas Compartment Block and LMWH

- 2 case reports of disastrous retroperitoneal hematomas requiring transfusion with associated neuropraxia
- Recommend follow guidelines similar to epidural analgesia

Peripheral Nerve Block and Anticoagulants

- Risk is associated with type of RA
  - Epidural > SAB > PNB
- PNB risk
  - Continuous > Single shot
Peripheral Nerve Blockade and Anticoagulants

- Risk increases with:
  - Technical difficulty of procedure
  - Increasing patient age
  - With combinations of anticoagulants

Applying ASRA Guidelines to PNB

- Consideration should be given for deep, non-compressible sites
- Even with deep blocks hematomas resolve or can be evacuated
- Reversible neuropathy trumps paraplegia any day

www.asra.com
INTRODUCTION

Nanotechnology is the art and science of manipulating nanometer scale (1-100 nm) materials in a microphysical realm where quantum physics effects are usually important.1 In this sense, nanotechnology is the engineering of molecular-level systems. It is a particularly varied field of scientific endeavor, ranging from relatively uncomplicated variations on existing products like paint and sunscreen to radical but as yet largely unproven (outside of nature) approaches based upon molecular self-assembly. Nanotechnology involves the application of fields of science as diverse as quantum physics, materials science, organic chemistry, molecular biology, semiconductor electronics, microfabrication, and mathematics. It is truly interdisciplinary in nature.

Inspiration for the field of nanotechnology is sometimes attributed to Nobel laureate physicist Richard Feynman who, at an American Physical Society meeting at Caltech on December 29, 1959, presented a lecture entitled, “There’s Plenty of Room at the Bottom,” where Feynman imagined a process by which individual atoms and molecules might be manipulated.2 Eric Drexler later took Feynman’s ideas and added the idea of computer control in his 1986 book Engines of Creation: The Coming Era of Nanotechnology.3 (Figure 1, above). See also Drexler’s web site at http://e-drexler.com for further information.

SCALES

One nanometer (nm) is one billionth, or $10^{-9}$ of a meter. Conventionally, nanotechnology is taken as covering the scale of 1 to 100 nm, the lower limit is set by the size of atoms while the more or less arbitrary upper limit of 100 nm is the size where material properties become increasingly macroscopic in behavior.

Some sizes of familiar entities may help provide perspective: the spacing between carbon atoms in an organic molecule is in the range 0.12–0.15 nm, a DNA double-helix has a diameter of approximately 2.5 nm, and the smallest cellular life-forms, the bacteria of the genus Mycoplasma, are around 200 nm in length. A red blood corpuscle is about 7 microns (micrometers) in diameter, or about 7000 nm.

NANOMEDICINE

Nanomedicine is concerned with the possible medical applications of nanotechnology, such as the use of nanomaterials for clinical purposes, as well as applications such as the development of nanosized biosensors, nanosized drug delivery systems (e.g., using polymer-based nanoparticles), and molecular nanotechnology approaches to detecting and treating disease. Current problems for nanomedicine also involve understanding the toxicity and environmental impact of nanoscale materials, as well as the use of nanotechnology to improve diagnostic imaging (Figure 3).

NANOPHARMACOLOGY

Nanopharmacology is a new and exciting interdisciplinary field involving delivery of pharmaceuticals through nanotechnology methods like the use of nanoparticles or liposomes. When designed to avoid destruction by immunological defense mechanisms (a field of active research), nanoparticles can be used to improve drug delivery, since cells take up these
nanoparticles because of their size, whereas larger particles end up being removed from the body.

**NANOROBOTS AND CELL REPAIR MACHINES**

Both science fiction writers and futurists have wondered about the possibility of using nanorobots (“nanobots”) for clinical purposes such as detecting/repairing cellular damage and fighting invading infectious organisms. Such nanodevices might even be imagined working inside the body using magnetic resonance imaging if 13C atoms rather than the natural 12C isotope of carbon is used, since 13C has a nonzero nuclear magnetic moment. The ultimate aim would either be cellular repair or, where that is not possible, to induce apoptosis. Some of the most critical challenges for such an initiative include [1] finding a means to power the device, [2] finding a means to control the device, and [3] ensuring that the device does not injure the patient in some unanticipated way. Figure 4 above provides an artist’s conception of a nanorobot injecting a red blood corpuscle with a drug. (Image Credit: http://www.sciencephoto.com/media/96509/enlarge

**SPECIAL STRUCTURES**

Research in nanotechnology has led to a number of developments in molecular configuration that show special promise. These include the buckyball, a spherical fullerene molecule with the molecular formula C_60 (Figure 5, left) as well as other fullerene molecules such as carbon nanotubes (cylindrical fullerenes, Figure 6, left). (The name “fullerene” was coined to honor Buckminster Fuller, whose geodesic domes it resembles.)

In the case of nanotubes, their special molecular structure results in particularly useful physical properties, such as high tensile strength and excellent electrical and heat conductivity. (Of interest, the chemical bonding of nanotubes is composed entirely of sp2 bonds, similar to those of graphite. These bonds provide nanotubes with their unusual tensile strength.)

**SAFETY**

A number of safety issues in relation to nanotechnology are being studied, as it not well known what happens when nanoparticles are dispersed into the environment. It is suspected, however, that nanoparticles of materials that are harmless at their full size may be harmful at sizes small enough to enter cell nuclei and “wreck havoc” by causing nuclear changes. On the other hand, it is exactly this possibility that has some nanotechnology researchers exploring as a novel means to overcome cancer drug resistance, since one of the tricks cancer cells use to evade anticancer therapy is by producing a protein that pumps drugs out of the cell before these compounds can exert their clinical effects. One idea is to use iron oxide-titanium dioxide nanoparticles to bypass this pump and enable cancer drugs to reach the cell nucleus.6

**REFERENCES**


**FURTHER READING**

(All papers are “Free Full Text” with no subscription barrier)


Anesthesiology is the safest of all medical disciplines, with a ‘failure’ rate of fewer than 1 in 10,000 cases. Our specialty has a history of interest in patient outcomes that dates back more than a century, and includes such landmarks as Rovenstine’s promulgation of collected anesthesia case records in the 1930s; Beecher and Todd’s examination of perioperative mortality in the 1950s; and creation of the Anesthesia Patient Safety Foundation, the Foundation for Anesthesia Education and Research and the Anesthesia Closed Claims Project in the 1980s. In 2000 the Institute of Medicine published To Err is Human, calling attention to preventable errors in healthcare and calling for a focused effort to improve. Anesthesiology was singled out as the medical discipline which had done the most to improve patient safety. In 2009 the American Society of Anesthesiologists took another step forward by founding the Anesthesia Quality Institute (AQI). The AQI’s mission is to improve patient outcomes through development of a national anesthesia registry.

The AQI was created in part because information technology has advanced fast enough to make a national case registry feasible, and in part because of a tidal wave of regulations bearing down on anesthesiologists and their practices. With increasing government subsidy of the US healthcare system – approaching 50% of all payments to hospitals and physicians – has come increased government interest in assuring good value for the money spent. This trend leads to the concept of ‘Pay for Performance,’ under which reimbursements will be tied to the healthcare outcomes achieved, rather than to traditional fee for service. Beyond that is a healthcare landscape dominated by Accountable Care Organizations (ACOs) and Medical Homes. While many details are hotly debated, the overall trend of healthcare financing towards bundled payments for specific outcomes (such as annual management of diabetes or diagnosis-to-recovery of cholecystitis) cannot be disputed. Anesthesiologists of the future will be required to document not just what they do (procedures) but also how effective it was (outcomes) if they wish to be paid. While this cultural shift is beneficial to us as taxpayers and patients, it will impose new and challenging regulatory hurdles on practicing physicians.

Every anesthesia practice or department needs a Quality Management (QM) program. While names and structure vary, the purpose of QM is for the group to understand its own practice and outcomes, to have a mechanism for managing adverse events, and to meet regulatory requirements imposed by the government or the facilities they work in. A detailed explanation of recommended practice QM activities can be found in the Manual for Anesthesia Department Organization and Management (MADOM), a comprehensive document produced by ASA for its members and available on the Society website. A more concise and concrete QM plan can be found on the AQI website at http://aqihq.org/qm-in-your-practice.pdf. The 8 recommended steps of this plan are summarized in Table 1.

### Table 1 – The 8 recommended steps for quality management in an anesthesia practice.

<table>
<thead>
<tr>
<th>Step</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Designate a physician to lead</td>
</tr>
<tr>
<td>2</td>
<td>Establish a list of indicators</td>
</tr>
<tr>
<td>3</td>
<td>Gather and record data</td>
</tr>
<tr>
<td>4</td>
<td>Report to the group and to local stakeholders</td>
</tr>
<tr>
<td>5</td>
<td>Review unusual events</td>
</tr>
<tr>
<td>6</td>
<td>Make improvements</td>
</tr>
<tr>
<td>7</td>
<td>Re-measure, and automate the process</td>
</tr>
<tr>
<td>8</td>
<td>Participate in a national registry</td>
</tr>
</tbody>
</table>

### What to Measure

Any number of performance measures can be created to describe the practice of anesthesiology, but each will require investment of resources to define, create, validate, analyze, and report. In real life, what we measure is determined by the following factors:

- What is incentivized
- What is locally important
- What is possible to collect

As irrelevant as they may be to an anesthesia-related patient outcome, the most commonly collected performance measures in our specialty are the three approved process measures of the Physician Quality Performance System (Table 2). This is a program of the Center for Medicare and Medicaid Services (CMS) that offers a financial incentive to physicians who can

### Table 2 – Measures applicable to operative anesthesia practice from the Physician Quality Reporting System.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>#30</td>
<td>Timely administration of prophylactic perioperative antibiotics.</td>
</tr>
<tr>
<td>#76</td>
<td>Central Venous Catheter insertion bundle. Successful performance includes hand washing, gown, gloves, mask, large sterile drape, and skin prep with chlorhexidine.</td>
</tr>
<tr>
<td>#193</td>
<td>Perioperative temperature management. For cases longer than 1 hour, either documentation of active warming efforts or patient temperature 36 degrees C or greater at case end.</td>
</tr>
</tbody>
</table>
document compliance with CMS approved measures. While any physician can theoretically submit data on any of the 300+ PQRS measures, in practice only these three apply to routine operative anesthesia. Although the financial rewards are small (an additional 1% reimbursement on Medicare cases in 2012), anesthesiologists have pressed their billing companies to facilitate this documentation because in 2015 the incentives will turn into penalties for non-compliance. Of the 4,000,000 cases in the National Anesthesia Clinical Outcomes Registry as of April, 2012, more than 75% included PQRS data.

PQRS measures for anesthesiologists are process surrogates known to be associated with the patient’s risk of developing a surgical wound infection. While this is an important outcome to both surgeons and patients it is unlikely to be the measure of greatest interest to anesthesiologists. The ASA is working to develop more relevant measures for public reporting that are based on actual outcomes, that reflect the core quality of anesthesia practice, and that apply to a majority of the patients we care for.

About 40% of all anesthesia practices collect “homegrown” performance measures that help them recognize improvements in care at the local level. The advantage of these measures is that they are developed out of local logistics (what data is easy to collect or report), local conditions (the kinds of surgical procedures done) and the local patient population. These private measures are very useful for assessing the performance of the group that develops them, especially when followed as trends over time. The disadvantage of these measures is that they are difficult to compare to other institutions.

One of the goals of the AQI is to increase consistency in quality measure definitions over time, in order to facilitate national aggregation. Table 3 shows an AQI-suggested template for local outcome capture, for completion at whatever time the practice has its last contact with the patient. Ideally this would be a bedside visit or phone call 24 hours after surgery, but more commonly today is at the time of PACU discharge. Definitions for the various complications listed are in a data dictionary on the AQI website, and are adapted from the efforts of the ASA Committee on Performance and Outcome Measures. This template for assessment has been adopted by a number of practices for clinical use, and by vendors of Anesthesia Information Management Systems (AIMS) and freestanding quality capture software.

**Table 3 – AQI recommended postoperative outcome capture.**

<table>
<thead>
<tr>
<th>CASE INFO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date_________ MR#_________ ASA Class_________</td>
</tr>
<tr>
<td>Anesthesia Type_________ Provider ID_________</td>
</tr>
<tr>
<td>CRNA ID_________ Additional Provider_________</td>
</tr>
</tbody>
</table>

**NO UNTOWARD EVENT**

- Significant Delay
- Unanticipated Hospital Admission
- Death
- Cardiac Arrest
- Perioperative MI
- Anaphylaxis
- Malignant Hyperthermia
- Transfusion Reaction
- New Stroke
- Visual Loss
- PONV

- Extended PACU
- Unanticipated ICU Admission
- Incorrect Surgical Site Complication
- Intraoperative Awareness
- Unrecognized Difficult Airway
- Unplanned Reintubation
- Dental Trauma
- Peripheral Neurologic Deficit
- Medication Error
- Hypothermia in PACU

- Case Cancelled
- Equipment Problem
- Vascular Access
- Infection After
- Epidural Hematoma
- High Spinal
- Postdural Puncture Headache
- Local Anesthesia Toxicity
- PACU Pain Control Inadequate

**HOW TO REPORT**

There is considerable heterogeneity in reporting of quality measures across anesthesia practices. A few groups gather patient outcome data from every case, and use this data to generate regular reports to their practitioners. Many more practices gather outcomes only by exception (i.e. when an adverse event is reported) and provide no regular feedback to the clinicians involved. Yet without analysis and reporting there is little utility to collection of data in the first place, a point which is frequently missed in the ongoing stampede to AIMS and electronic records in general. The present landscape in anesthesia QM reflects an ongoing paradox: we have invested millions in digitizing and aggregating our clinical data, but have not taken the time to analyze what we’re collecting or put it to work to improve our practice. As one frustrated Anesthesia Department Chair recently noted: “We bought a very expensive typewriter.”

Efficient use of data requires careful consideration of the context in which it is collected, and the intended purpose of reporting. At one end of the spectrum is reporting intended to improve individual clinical care, one anesthesiologist at a time. These reports are best kept absolutely confidential. Personal data is shown as a trend over time—typically quarters or years, to include sufficient numbers of cases—and is most useful when compared to practice-wide norms or to the performance of other individuals (shown as data points but not
identified). Because the comparisons are local, less risk adjustment or heavy statistical processing is necessary. As the only recipient of the report, the individual provider already has a good understanding of how and where the data is collected, and how seriously to take the results. Simple feedback in this way can have a powerful effect on outcomes; every physician is motivated to do a good job for every patient, and will naturally gravitate towards improvement if a measuring stick is provided.

Reporting at the practice or facility level is appropriate for less common events, such as the rate of serious adverse outcomes, or for events which are difficult to attribute to individual providers, such as unexpected admission after an outpatient procedure. Risk adjustment is not necessary if the patient and surgical population is remaining relatively constant over time. This kind of reporting is ideal for ongoing surveillance of quality and business efficiency issues (such as on-time first case starts) and lends itself to analysis and presentation in a control chart format that shows when a process is remaining stable and when it is improving or deteriorating.

Public reporting of local QM data for purposes of regulatory compliance and transparent communication with external stakeholders is a scary proposition for most anesthesia quality managers, because of the serious risk of unintended consequences when outcomes are compared between different practices. Apple to apple comparisons require common definitions of all variables, standard methods of data collection, active validation and auditing, and complex risk adjustment models. A detailed discussion of this topic and the issues it creates can be found in a recent publication by Glance et al in Anesthesia and Analgesia.

Aggregate national reporting of anesthesia outcomes is a core purpose of the AQI. Understanding what we do, and how we do it, will be essential for influencing future regulatory efforts and designing educational products. Collecting, validating and analyzing data from practices across the country will be an endless task, especially with the advance of digital technology and the ever-increasing reach of electronic healthcare records. The AQI is off to a good start, with more than 4,000,000 individual case records in hand as of April 2012, and a steadily accelerating rate of practice participation. With about 7-10% of all anesthetics now appearing in the National Anesthesia Clinical Outcomes Registry, the AQI has the power to paint a representative picture of our specialty. Figure 1 describes our patients. Figure 2 describes our practice locations and the type of work we do. Figure 3 shows our outcomes, in very broad strokes. The annual AQI publication Anesthesia in the US, which includes these figures and many other national descriptors of anesthesiology, is made available at no charge through the AQI website to ASA leaders and participating practices, and for a nominal fee to all others.

<table>
<thead>
<tr>
<th>Measure Group</th>
<th>Description (n=814,890 cases)</th>
<th>Events</th>
<th>Incident Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process</td>
<td>Process Failure: PQRS and SCIP measures</td>
<td>11,201</td>
<td>1.37%</td>
</tr>
<tr>
<td>Major</td>
<td>Serious adverse events: actual patient harm or significant risk</td>
<td>3,539</td>
<td>0.43%</td>
</tr>
<tr>
<td>Minor</td>
<td>Minor adverse event: without long-term impact</td>
<td>85,210</td>
<td>10.46%</td>
</tr>
<tr>
<td>Admin</td>
<td>Administrative failure: e.g. case cancelled, extended PACU stay, unexpected admission</td>
<td>11,420</td>
<td>1.40%</td>
</tr>
<tr>
<td>Mortality</td>
<td>Patient death: (excludes patients presenting for organ harvesting)</td>
<td>293</td>
<td>0.04%</td>
</tr>
</tbody>
</table>

**WHAT THE FUTURE HOLDS**

While the fate of the Affordable Care Act is uncertain at this time, there is little doubt that some kind of healthcare reform will be necessary to address spiraling costs. Elimination of waste through alignment of incentives will likely dictate increasing ‘bundling’ of care, with payment for outcomes rather than procedures. Anesthesiologists who wish to prosper under this model will be required to take an aggressive role in managing patient flow throughout the perioperative period. ASA has developed plans...
and models for the “Perioperative Surgical Home,” and is partnering with willing anesthesia practices to test and validate this concept. Collection and reporting of outcome measures will be essential to this concept, to assure that patient safety is not sacrificed in pursuit of more cost-effective care.

Intertwined with the national landscape of healthcare reform is an ongoing evolution in anesthesia practice models. Although we train as inpatient providers and think of ourselves as hospital-based, data from NACOR shows that more than 60% of all anesthetics occur in outpatients. New practice models have arisen to account for a surging demand in office-based care and procedural sedation. While the value of anesthesia to facilitate routine diagnostic procedures in healthy patients is debatable, there is little doubt that we will be increasingly called on to support advanced non-surgical procedures in the cath lab, invasive radiology and the GI clinic, and to care for patients with high levels of medical complexity. The median anesthesia practice in NACOR currently provides service at 9 different facilities, and this number is likely to rise. Tracking the evolution of anesthesia practice models in size, scope and coverage patterns will be important to the profession going forward.

Medication shortages are a new, but almost universal, issue in clinical anesthesia. There are myriad causes for drug shortages but few easy solutions, so this may remain an aspect of anesthesia care for some time to come. There will be a need for data on the demographics of medication supply and even more so for outcome information that reflects the consequences. These will range from the trivial (prolonged PACU stay based on unavailability of muscle relaxants) to the potentially lethal (unavailability of pressors for resuscitation). This data will be applied to advocacy efforts with pharmaceutical companies and the government, and to development of educational material ranging from practice guidelines to residency curriculum to simulation exercises that help anesthesiologists maintain patient safety.

CONCLUSION
These are dynamic times in healthcare in general and anesthesiology in particular. The purpose of a good QM program is to provide the data needed to improve patient care and drive business efficiency. This is an investment that every practice and department must make, if we are to maintain our status as the leaders in patient safety.

REFERENCES
Perioperative Fluid Management: Aquatic Assassins?

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INTRODUCTION

Fluid management is an essential part of patient care in the perioperative period. Adequate plasma volume is vital in maintaining cardiac output and hence tissue perfusion. Inadequate tissue perfusion is associated with poor outcome following surgery.¹ Fluid management strategies have undergone several shifts over the past fifty years. Prior to the sixties, fluid restriction during the intraoperative period was widely practiced. In the early 1960s, it was demonstrated that major surgery and trauma were associated with fluid requirements that significantly exceeded the usual rate of fluid maintenance.² As a result, fluid administration became less restrictive. A decade later, the choice of fluid became the subject of intense debate, and continued till today, as colloid versus crystalloid controversies are still raging on. In the late eighties and early nineties, the concept of achieving a “supranormal” oxygen delivery attracted much interests. More recently, goal directed fluid management appear to show benefits in surgical settings. The last few years saw the development of new colloid solution, with its physical characteristics and its “balanced electrolyte” carrier.

FLUID COMPARTMENTS

Accurate replacement of fluid deficits requires an understanding of the distribution volume of body fluids. For a person weighing 70 kg, total body water (TBW) is about 42 L. The total body water exists within discrete but dynamic fluid compartments. Two thirds of the TBW (28 liters) is intracellular water. The remaining third (14 liters) in the extracellular compartment is divided into the intravascular (5L) and extravascular (9L) compartments. Blood is composed of around 60% plasma (extracellular compartment) and 40% red and white blood cells and platelets (intracellular compartment). Plasma consists of inorganic ions (predominantly sodium chloride), simple molecules such as urea and larger organic molecules (predominantly albumin and the globulins) dissolved in water. Interstitial fluid bathes the cells and allows metabolic substrates and wastes to be diffused between the capillaries and cells in the tissue. Excess free interstitial fluid enters the lymphatic channels and is ultimately returned to the plasma. The majority of the interstitial water exists within a proteoglycan matrix in a gel form. The “transcellular fluids” are extracellular and extravascular and include the cerebrospinal fluid, aqueous humor, pleural, pericardial, peritoneal and synovial fluids.

The cell wall separates the intracellular compartment from the extracellular compartment. The capillary endothelium and the walls of arteries and veins divide the extracellular compartment into the intravascular and the interstitial (tissue or extravascular) compartment. Water moves freely through cell and vessel walls and distributes throughout all these compartments. The energy dependant Na+ /K+ ATPase in cell walls excludes Na+ and Cl- ions and maintains a sodium gradient across the cell membrane: Na+ is an extracellular ion. The capillary endothelium is freely permeable to small ions such as Na+ and Cl-, but is relatively impermeable to larger molecules such as albumin and the semi-synthetic colloids e.g. gelatin and starches which are maintained in the intravascular space. The protein and synthetic colloids therefore exert a colloid oncotic pressure (COP) which serves to retain plasma water within the intravascular compartment.

Colloid Oncotic Pressure and Fluid Flux

Colloid Oncotic Pressure (COP) is the osmotic pressure exerted by the macromolecules (the colloid molecules). Solute that can pass freely across a semi-permeable membrane do not generate any oncotic pressure - they are effectively a component of the solvent with respect to that membrane. Where membranes are selectively permeable to solutes the water content of the fluid compartments is dictated by solute distribution as water moves down any osmotic pressure gradient to produce isotonicity. The COP of the plasma is only one of several forces determining fluid flux at the vascular membrane. Starling in 1896 first described the forces affecting the flux of fluid across the capillary membrane.³ These forces can be expressed in the following equation:

\[ QV = K [(\pi C - \pi T) - \alpha C (\pi C - \pi T)] \]

in which \( QV \) = total flow of fluid across the capillary membrane; \( K \) = fluid filtration coefficient; \( PC \) = capillary hydrostatic pressure; \( PT \) = interstitial hydrostatic pressure; \( C \) = reflection coefficient; \( \pi C \) = capillary COP (plasma); \( \pi T \) = interstitial COP. The filtration coefficient is a function of the permeability and surface area of the capillary bed in question. The numeric value represents the net volume of fluid crossing the capillary membrane under a specific set of conditions. The reflection coefficient is a mathematical expression (from 0 to 1) of the capillary membrane’s permeability to a particular substance. Thus the reflection coefficient will vary with both the tissue bed and substance in question. If a substance is completely permeable to the capillary membrane, the reflection coefficient will be 0; if it is totally impermeable, the coefficient will be 1.
For protein, the approximate reflection coefficients for liver, lung, and brain are 0.1, 0.7, and 0.99, respectively.\(^1\) When a pulmonary insult creates a leaky capillary state, the protein-lung reflection coefficient may decrease to approximately 0.4.\(^5\) The reflection coefficient for albumin, the source of 60% of the normal oncotic pressure in the pulmonary circulation, is approximately 0.7.

The composition of administered fluids will therefore dictate their distribution. Pure water expands all body fluid compartments and therefore provides minimal expansion of the intravascular volume. Intravenous infusion of an isotonic solution of sodium chloride expands only the extracellular compartment and will increase intravascular volume by about one fifth of the volume infused. Colloidal solutions containing large molecules are maintained within the circulation, at least initially, and so provide greater intravascular volume expansion per unit volume infused. Lamke and Liljedahl,\(^6\) demonstrated that 90 minutes following infusion of 1000 mL of 6% hetastarch, albumin or saline in postoperative surgical patients, 75% and 50% of the hetastarch and albumin respectively, still remain in the intravascular space, whereas only less than 20% of saline remained.

**CHOICE OF FLUIDS**

The choice of intravenous fluids may broadly be categorized as colloids and crystalloids. Crystalloids are effective and appropriate for the initial management of extracellular compartment losses associated with hemorrhagic shock, major surgery or trauma. After this acute resuscitation phase, there usually is a significant degree of hemodilution and a diminished plasma COP.\(^7\) This reduction in plasma COP has been associated with the development of edema and transudates. It is therefore appropriate that continued fluid resuscitation should include colloid solutions in an attempt to minimize interstitial edema within vital organs e.g. heart, lung and brain. Colloids are defined as having larger molecular weight and hence would remain in the vascular space for a longer period of time. Colloid-containing resuscitation protocols have been demonstrated to have the ability to either maintain or increase the plasma COP.\(^7\) Colloids available in the US include synthetic starches, albumin and dextran.

**Hydroxyethyl Starch**

The hydroxyethyl starch (HES) compounds are a group of polydisperse synthetic colloids that resembles glycogen structurally. Hetastarch is a high molecular weight HES, with an average molecular weight of 450,000 d with 80% of the polymers falling in the range of 30,000 d to 2,500,000 d. However, for polydisperse colloids, the number-average molecular weight (MWN) provides a better representation of the number of particles of a given size as opposed to the weight-average molecular weight. Hydroxyethyl starches are synthesized from amylopectin, a waxy starch derived from maize or sorghum. Amylopectin is a D-glucose polymer with a branching structure. Reaction with ethylene oxide in the presence of an alkaline catalyst results in hydroxyethyl substitution. The majority of these substitutions occur at carbon 2 in the glucose ring with the rest occurring at carbon 3 and 6. Increased C2/C6 substitution ratio results in slower enzymatic degradation.\(^8\) The unsubstituted starch is rapidly hydrolyzed by non-specific α-amylases in the plasma and substitution with hydroxyethyl groups substantially slows this process. The degree of substitution (DS) indicates the proportion of glucose moieties that have been substituted and is expressed as a number from 0-1. Starches with a DS close to 1 have a greater resistant to hydrolysis than those with a lower DS. The substituted starch is then refined into the final product by hydrolysis to the required molecular weight, purification and for certain products a fractionation process to produce specified molecular weight bands. Hetastarch is primarily excreted via the kidneys. Particles weighing less than 50,000 d are rapidly filtered through the kidneys while particles with 40%-50% of the administered dose eliminated within 48 hours.\(^9\)

Pentastarch is a smaller molecular weight molecule with an average molecular weight of about 200,000. It has a shorter half-life and does not seem to affect the reticulo-endothelial system. Pentastarch 10% has a good initial volume-expanding capacity of 1.2 times the infused volume. About 90% is eliminated within 24 hours and most is undetectable after 96 hours. Recently, Voluven, a third generation low molecular weight hetastarch (140kD/0.4) was approved in the USA.

**Albumin**

Albumin is a naturally occurring plasma protein composed of 584 amino acid residues. The molecular weight of albumin ranges from 66,000 to 69,000 depending on the technique of measurement.\(^10\) The molecule is highly soluble and carries a strong negative charge at physiological pH. Consequently, albumin migrates in the electrical fields. Depending on the salt and buffer concentration of the plasma, albumin is isoelectric in the pH range of 4.4 and 5.4. In serum, albumin is in part bound to either cations or anions. This property accounts for its role as a carrier protein for the transport and activation of drugs, hormones, enzymes, fatty acids, amino acids, bilirubin and other metabolites. The half-life of circulating albumin is approximately 18 to 20 days. Albumin provides approximately 70% of the plasma colloid oncotic pressure in normal human subjects. Human albumin is available for infusions as either 5% or 25% solution. The 5% solution is approximately iso-oncotic with that of normal subjects, whereas the 25% solution is markedly hyperoncotic. Human albumin is prepared from human plasma following a heating process for 10 h at 60°C.

Plasma protein fraction (PPF) is a 5% solution of selected proteins prepared from pooled human blood, serum, or plasma. It undergoes the same pasteurization process used for albumin and is a mixture of proteins consisting mostly of albumin in an amount equal to...
or greater than 83% of the total protein composition. Although albumin solution may be more purified and contains a greater percentage of albumin (>93%), the two solutions are similar in costs, and hence are used interchangeably.

Dextrans

Dextrans are high molecular weight D-glucose polymers linked by alpha1,6 bonds into predominantly linear macromolecules. They are biosynthesized commercially from sucrose by the B512 strain of Leuconostoc mesenteroides using the enzyme dextran sucrase. This produces a high molecular weight dextran that is then cleaved by acid hydrolysis and separated by repeated ethanol fractionation to produce a final product with a relatively narrow molecular weight range. The products in current clinical use are described by their MWN: Dextran 40 and Dextran 70 having MWns of 40,000 and 70,000 dalton respectively.12

Infusions of hyperosmotic-hyperoncotic solutions such as hypertonic saline dextran has been shown to be very effective in expanding plasma volume rapidly. The intravascular volume expansion efficiency, defined as milliliter plasma expansion/milliliter fluid infused was 7 and 20 folds at 30 and 60 min after infusion, respectively when hypertonic saline dextran was compared with lactated Ringer’s solution (LR).13

SALINE VS. “BALANCED” ELECTROLYTES BASED FLUIDS

Colloids and crystalloids may be divided into whether they are formulated in 0.9% sodium chloride or a variety of balanced electrolyte solutions. Lactated Ringer’s and Normosol solutions consist of a number of electrolytes that are present in the plasma, whereas 0.9% saline is made up of only sodium and chloride. There appears to be differences between saline vs. balanced electrolyte based solutions when used clinically.

Acid Base balance and renal outcome

In a human volunteer crossed-over study, Williams and colleagues found a significantly higher incidence of subjective mental changes, abdominal discomfort, as well as a significant delay of time to first urination, in the group that received 50 mL/kg of 0.9% sodium chloride over 1 hr compared with the same volume of lactated Ringer’s solution, along with a transient decrease in blood pH. Scheingraber et al. demonstrated a significant hyperchloremic acidosis at the end of surgery in patients undergoing major gynecological hysterectomies when 0.9% sodium chloride was used as the intraoperative resuscitative fluid.15 In a recent study of geriatric surgical population undergoing major non-cardiac surgery, the perioperative use of balanced electrolyte solutions (Hartmann’s solution and Hextend) was associated with significantly lower incidence of hyperchloremic metabolic acidosis (0% versus 66%) in saline group and better gastrointestinal mucosa perfusion compared with sodium chloride based solutions (0.9% saline and Hespan). Other studies have demonstrated the predictability of acidosis following intraoperative administration of saline based fluid.16-19

HEMOSTATIC EFFECTS OF COLLOIDS

The choices of fluid administered intraoperatively can result in differences in the coagulation effects. Hespan in larger volume (>20 mL/kg) has been associated with reduced levels of the coagulation factors, e.g., fibrinogen, Factor VIII, and von Willebrand’s factor and reduced platelet function, beyond the effect of hemodilution. This has prompted the FDA to issue a warning against high volume administration in its package insert. Crystalloid administration, however, is associated with a hypercoagulative state.20

A recent study demonstrated a better thromboelastographic (TEG) coagulation profile when larger volumes of Hextend® (>20 mL/kg) was used compared with equivalent volumes of 6% hetastarch in saline (Hespan).21 Hespan was associated with a hypocoagulable state with prolongation of both their r time and k time and a reduction in MA on thromboelastography. This hypocoagulable state continued into the first 24 hours postoperatively.22 LR solution, however, was associated with a hypercoagulable state.22,23 The TEG profiles with respect to Hextend® showed the least change.22 When used for acute normovolemic hemodilution, hetastarch and dextran appeared to attenuate the hypercoagulative state seen when LR and albumin were used.24 In another study when Hextend was compared with albumin, there appeared to be no differences in the levels of Factor VIII, von Willebrands factors and platelets up to 24 hours following major surgery.25 Boldt et al. compared a high molecular weight hydroxyethyl starch (Hextend), a low molecular weight hydroxyethyl starch (130kDa, DS=0.4) and lactated Ringer’s in patients undergoing major abdominal surgery. The patients in the Hextend group experienced more blood loss, and needed more blood and blood products, compared with the other two groups. Interestingly, the standard coagulation tests (PT, APTT and platelets) showed no significant differences between the groups up to 2 days following surgery.26

GOAL DIRECTED FLUID ADMINISTRATION

Since the late 1950’s a succession of authors have described an association between perioperative cardiac output and survival following major surgery: the survivors exhibiting higher values than the non-survivors.27-29 From these observations the hypothesis developed that using the cardiac output and oxygen delivery values exhibited by the survivors, as goals for all patients would reduce overall mortality.27 In 1988 Shoemaker et al.30 demonstrated that targeting specific values for cardiac index, oxygen delivery and oxygen consumption, using fluids and inotropes to achieve these goals, resulted in a reduction in mortality and morbidity.
Since then a number of single center randomized controlled trials have been conducted, the majority of which support this original positive result. Five studies have used the same hemodynamic goals as the original study by Shoemaker. Two of these were large (>100 patient) studies on high-risk general surgical and vascular patients and both demonstrated a statistically significant reduction in mortality in the protocol groups.\textsuperscript{31,32} Two were studies of major trauma surgery and these were both conducted by the same group.\textsuperscript{33,34} The first smaller study showed a trend towards reduction in mortality in the protocol group and this was confirmed by a statistically significant reduction in protocol group mortality in the second, larger trial. The fifth study in this group was a small trial focusing on surgery for hepatobiliary carcinoma and demonstrated a reduction in liver failure and hyperbilirubinemia although this was not their specified primary outcome variable.\textsuperscript{35} An older study using a similar philosophy, but with less clearly defined goals, in patients undergoing hip fracture surgery also demonstrated a significant mortality reduction.\textsuperscript{36} Somewhat different results have been obtained in a series of papers in which patients presenting for major vascular or aortic surgery were studied.\textsuperscript{37-39} The goals for cardiac index and oxygen delivery used in these trials were significantly lower and the overall mortality for each trial was also low. These studies did not demonstrate a significant reduction in mortality, or in some cases complications, however in only one of these studies were there more deaths in the protocol than control groups.\textsuperscript{37}

Targeting mixed venous oxygen saturation (SvO2) as an indirect index of oxygen delivery has also been studied in two trials. The first studied patients having aortic or lower limb arterial surgery and failed to demonstrate a significant morbidity or mortality difference between control and protocol groups.\textsuperscript{40} More recently a large Scandinavian study of patients undergoing elective coronary revascularization with cardiopulmonary bypass demonstrated a significant reduction in length of stay in those randomized to maintenance of SvO2 > 70% and lactate ≤ 2 mmol•L\textsuperscript{−1} when compared with controls.\textsuperscript{41}

A number of published studies using intraoperative esophageal Doppler monitoring of cardiac output compared a stroke volume optimization algorithm with standard fluid management. In the first study patients with normal left ventricular function undergoing coronary artery revascularization had a statistically significant reduction in length of stay in those randomized to colloids in combination with crystalloids.\textsuperscript{42} The second study, of elderly patients having hip prosthetic surgery also demonstrated a reduction in hospital length of stay in patients managed in the protocol group.\textsuperscript{43} Gan and colleagues, in a recent study using a similar optimization algorithm demonstrated a reduction in hospital stay and earlier return to tolerating solid food in the protocol group undergoing major non-cardiac surgery.\textsuperscript{44} Conway et al also demonstrated a lower incidence of ICU admission in the goal-directed fluid therapy group.\textsuperscript{45}

The application of this management approach to patients with established critical illness has been much less successful. A number of single center studies\textsuperscript{46-49} and one large multi-center RCT 50 have failed to show an outcome benefit for patients in the protocol group. Indeed in some studies the intervention group mortality exceeded that of the control group.\textsuperscript{47}

**COLLOID VS CRYSTALLOIDS**

Arguments over the best type of fluid for volume resuscitation have raged for more than 30 years. While all sides agree that fluid resuscitation is fundamental in the management of hypovolemia there is disagreement as to which solutions to use. Crystalloid supporters point to the hemostatic derangement, the increased incidence of adverse drug reaction and the greater risk of fluid overload occurring with colloidal fluids. The colloid lobby focuses on the large volumes of crystalloid required to achieve adequate resuscitation and on the resultant tissue edema and reduction in tissue oxygen delivery. A large number of RCTs have attempted to address this question in a number of clinical settings. There have been three meta-analyses focusing specifically on this issue with mortality as the endpoint.\textsuperscript{51-52} The most recent of these focused on 19 RCTs including 1315 patients and suggested an increase absolute risk of mortality of 4% with use of colloid for volume replacement (95% confidence interval 0% to 8%). However these meta-analyses have been widely criticized for pulling together a large number of studies comparing a number of different solutions amongst diverse patient populations, for varying indications. None of the original studies used mortality as a primary end point, the vast majority of studies included are of albumin or dextran solutions and these two colloids contribute all the excess mortality. At present there is a lack of adequate studies upon which to base a judgement on this question and many clinicians continue to use colloids in combination with crystalloids.

However, a recent study suggests that the quality of recovery may be superior when colloid/crystalloid combination was used compared with crystalloid alone in patients undergoing major non-cardiac surgery. Patients who received lactated Ringer’s alone had higher incidence of nausea and use of rescue antiemetic, double vision, and complained of more severe pain postoperatively.\textsuperscript{53}

**SUMMARY**

Perioperative fluid management has undergone significant advances over the past few decades. The choice of fluid and its electrolyte composition are important considerations when replenishing plasma volume and other body fluid compartments. The coming decade will likely see an expansion of knowledge defining the role of goal directed fluid therapy in clinical practice and the differences between colloids and crystalloids when used in the perioperative period.
REFERENCES