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Making Quality Metrics Work for Your Patients (and You)

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Since the beginning of organized medicine, patient safety has been a primary goal of practitioners. "First do no harm" articulates the understanding that action, or inaction, by caregivers can be associated with not only favorable effects but also patient harm. Yet, despite well-intentioned efforts to provide optimal patient care, an Institute of Medicine report in 2000 suggested that nearly 100,000 patients die from preventable medical errors each year.[1]

The public release of performance data has been proposed as a mechanism for improving quality of care.[1–5] Such reporting may improve patient care by identifying areas of under-performance and allowing for targeted improvement efforts. This information may also serve to improve quality of care as a result of efforts to maintain a market share for specific health care services or providers. Quality of care may have direct financial impact on providers as well. Multiple studies have linked improved quality of care with decreased costs.[6] Furthermore, the Centers for Medicare and Medicaid Services (CMS) initiated a quality reporting effort several years ago. Each year the requested metric set has increased, there are 27 for fiscal year 2008, and this information is used to determine the amount of payment at risk for nonparticipating hospitals.[4]

Accurately measuring quality of care is difficult. Patients variables such as underlying health and associated risk affect outcomes data for a given disease management strategy, thus outcomes should be risk-adjusted for comparison purposes. Obtaining data required for risk adjustment requires significant resources and is imprecise due to potential unknown risk factors. As a result, quality of care is increasingly being measured by adherence to practice guidelines. The nature of the practice of anesthesiology and perioperative medicine determines that compliance with practice guidelines is the manner by which most anesthesiologists will interface with quality metrics.

There are already several reportable quality metrics under the direct control of anesthesiologists. New metrics are frequently proposed, many of which impact the practice of anesthesiology. While some evidence questions if publishing patient care performance data actually improves quality of care,[7] quality metrics seem destined to remain a component of health care evaluation. To illustrate how current practice is shaped by such activities, a patient admitted for elective surgery will be followed through a typical perioperative course and current and proposed quality metrics described. The description is not intended to be exhaustive but is current at the time of submission.

A 67-year-old male presents for elective open abdominal aortic aneurysm repair. He has a history of coronary disease having presented with an acute myocardial infarction 1 year ago. Management during his myocardial infarction met hospital quality measures including administration of an aspirin and β-adrenergic blocker on hospital arrival and a percutaneous coronary intervention within 120 minutes of presentation.[2,5,7] He was discharged on an aspirin, a β-adrenergic blocker and an angiotensin receptor blocker in the setting of left ventricular systolic dysfunction (also reportable quality measures).[2,5,7] His history is also notable for diabetes managed by subcutaneous insulin administration. His primary physician has provided care consistent with the 2008 Physician Quality Reporting Initiative Professional Quality Measures pertinent for care of diabetic patients as his most recent hemoglobin A1c is $<9.0\%$, low density lipoprotein is <100 mg/dL, blood pressure is $<140/80$ mm Hg, and he has received screening for diabetic retinopathy, peripheral neuropathy, and lower extremity ulcer prevention.[8]

The patient is approved for anesthesia and presents for surgery. He is correctly identified and confirms understanding of the procedure about to be performed. After bringing the patient to the operating room, a low-thoracic epidural catheter is placed for intra- and postoperative use. Appropriate monitors are applied and anesthesia induced without event. A central venous catheter is then placed. In accordance with multiple health care quality initiatives, those whose practice involves the use of central venous catheters have previously received education regarding catheter-related blood stream infections (CRBSI) and the necessity of prevention. During catheter insertion, hand hygiene was performed prior to beginning the procedure AND skin antisepsis was accomplished using 2% chlorhexidine AND the femoral site was avoided AND maximal barrier precautions (cap AND mask AND sterile gown AND large sterile sheet) maintained.[4,5,8–11] Cefazolin is administered within 60 minutes of incision for surgical site infection (SSI) prophylaxis.[4,5,8–11]

During the case, blood loss anemia is managed by transfusion of red blood cells. To improve the accuracy of patient identification, bar coding is used to match the patient to the blood product. The use of this automated identification technology has obviated the need for two-person identification as had previously been performed.[9] Following completion of the case, all instrument and device counts are correct suggesting that there are no retained foreign bodies.

The patient is subsequently admitted to the intensive care unit (ICU) for postoperative management. In accordance with the ventilator-associated pneumonia bundle, the patient's head of bed is elevated to greater than 30 degrees, stress ulcer prophylaxis is achieved with a proton pump inhibitor and deep vein thrombosis (DVT) prophylaxis achieved with sequential compression devices. Due to the high bleeding risk immediately postoperatively, chemical DVT prophylaxis has been deferred during the initial postoperative period but initiated within 24 hours.[2,5,8,9] Removal of the epidural catheter is planned to occur 48–72 hours after placement and coordinated with chemical DVT prophylaxis administration.[12]

This brief scenario serves to highlight multiple quality metrics that directly impact anesthetic management. It should be apparent that most quality metrics bridge several areas of practice and require coordinated efforts to be successfully implemented. For example, the administration of chemical DVT prophylaxis and management of a neuraxial catheter needs to be coordinated.[12] Nonemergent central venous catheters placed in the operating room should adhere to best practice guidelines for catheter insertion, however daily assessment of catheter need and prompt removal of unnecessary catheters[4,5,8–11] is perhaps even more crucial to limiting CRBSIs. This daily assessment of need often relies on individuals outside of the anesthesia department and a lapse in this aspect of management may well negate any benefit of following best practice guidelines during catheter insertion.

Another example which is likely more familiar to readers is the administration of antimicrobial therapy for surgical site infection prophylaxis. The documented time of antibiotic administration is one widely reported quality metric.[4,5,8–11] Administration of antibiotics within 60 minutes of incision (save for fluoroquinolones and vancomycin) is most reliably performed by the anesthesia team working in concert with the surgical team. Less widely appreciated by practitioners is the requirement of institutions to share surgical site infection rate data and prevention outcome measures with their clinicians.

Many proposed quality metrics were not included in the scenario. For example, optimal glycemic management during the perioperative period is controversial. While multiple studies have shown an association between hyperglycemia and adverse outcomes in certain patient populations, including the critically ill,[13] available data to date do not suggest improved outcomes with strict intraoperative glycemic control.[14] Reportable metrics for perioperative glycemic control are currently restricted to cardiac surgery patients and limited to the glucose determinations closest to 0600 on the first 2 days following surgery.[5,9,11]

In summary, quality metrics are one way to describe the quality of care provided to patients. Many of the care processes measured occur during the perioperative period. It is crucial for anesthesiologists to understand current and proposed metrics and how they represent best practice in order to provide optimal care delivery. Quality metrics should be viewed as a means to enhance best practice in the care of patients. Anesthesiologists need to remain engaged in this process such that our best practices are integrated into more global initiatives.

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Anesthetic Management of Patients with Heart Disease Undergoing Noncardiac Surgery

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In the first 30 years of this century, the number of Americans greater than 65 years of age will double, resulting in over 70 million older individuals (Fig. 1). Other industrialized nations are experiencing a similar graying, and individuals over the age of 60 years have twice the incidence of symptomatic cardiac disease compared with younger patients.[1] In addition, the number of adults with congenital heart disease has increased dramatically in the past few decades due to advances in surgical treatment and medical management.[2] Currently, they number over a million. Thus, anesthesiologists will care for an increasing number of patients with heart disease, including patients having procedures in locations formerly restricted to exclusively healthy individuals, such as ambulatory surgery centers, radiology, and endoscopy suites.

This lecture will describe a physiologic approach to planning anesthetic management for patients with heart disease. It is not a cookbook approach. Indeed, the underlying assumption of this approach is that the choice of anesthetic technique or dose is quite secondary provided appropriate hemodynamic goals and surgical requirements are attained. During my lecture, I will illustrate the use of this approach with a few case examples.

OVERVIEW

In patients with heart disease, I recommend a four-step approach to planning anesthetic management: definition of cardiovascular pathology, prediction of the physiological compensation, determination of hemodynamic goals, and anticipation of hemodynamic emergencies and their treatment (Table 1). In these lecture notes, I will outline these steps and provide three case examples for your consideration. In my lecture, I will review the four steps and use them to determine anesthetic management plans for the case examples. If possible in advance of my lecture, please review the cases and outline how you would manage these patients in your own practice. They are real case examples.

DEFINITION OF CARDIOVASCULAR PATHOLOGY

Hemodynamically significant abnormalities of blood flow through the heart and great vessels must be understood in order to begin a rational approach to planning anesthetic management. Most cardiovascular pathology falls into three general categories: obstruction to blood flow, regurgitation of blood flow, and shunting of blood flow. For instance, obstructions include coronary artery or valvular stenosis. Most obstructions are fixed (e.g., aortic stenosis), but some can vary (e.g., right ventricular obstruction in tetralogy of Fallot and left ventricular obstruction in hypertrophic cardiomyopathy). The severity of the obstructions should be defined, if possible. Fortunately, a history of good exercise tolerance (greater than 6 metabolic equivalents) usually rules out the possibility of severe obstructions to flow. I usually ask whether a patient can climb a flight of stairs carrying groceries (about 5–6 metabolic equivalents). If at all possible, try to corroborate this history with family members or others who know the patient well. In my experience, some patients, especially men, tend to over estimate their exercise ability. In the absence of a convincing history of moderate to good exercise tolerance, additional testing should be considered if you anticipate that the results of the testing will affect the care of the patient. In 2007, the American Heart Association and the American College of Cardiology updated their guidelines on perioperative cardiovascular evaluation and care.[3] They recommend proceeding with surgery without further testing if the patient has good exercise tolerance ($\geq$ 4 metabolic equivalents) unless the patients has any of the following: unstable angina, recent myocardial infarction, decompensated heart failure, significant arrhymthmias, or severe valvular heart disease.

Regurgitation of flow is a valvular problem usually identified by auscultation. Again, the degree of exercise tolerance gives a guide to severity, but the chest radiograph will often be of additional help. For instance, severe aortic and mitral regurgitation lead to marked pulmonary vascular changes and cardiomegaly.

Shunting of flow can occur at four anatomic levels: atrial, ventricular, great vessel, or peripheral. Shunting abnormalities include atrial septal defects, ventricular septal defects, patent ductus arteriosus, and arteriovenous malformations. The size of most shunts is fixed (e.g., atrial septal defects), but some may be variable (e.g., the ductus arteriosus in newborns). Usually, the patient or his past medical record will reveal the results of prior cardiac evaluation with definition of shunt level

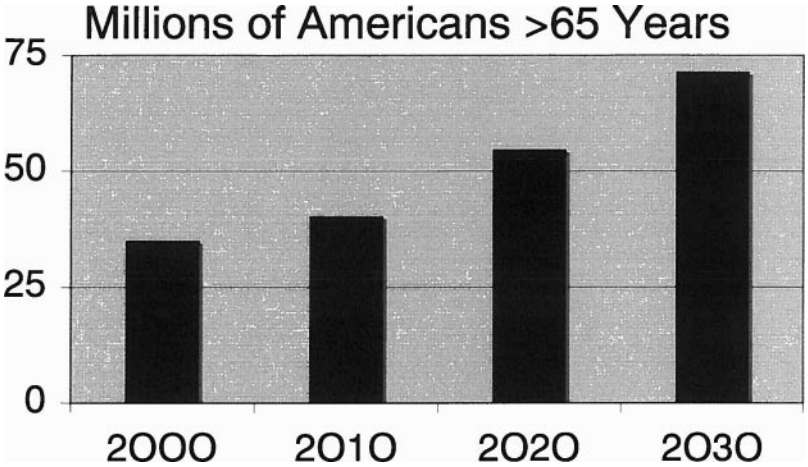

Figure 1. The number of individuals living in the United States who are over 65 years of age in the year 2000 and projected numbers for the years 2010–30. Data were taken from the United States Census Bureau tables.*

Table 1. Management Steps in Patients with Heart Disease

1. Define the cardiovascular pathology
2. Predict the physiological compensations
3. Determine the hemodynamic goals
4. Anticipate the cardiac emergencies and their treatment

and size. The most feared complication of shunts is severe pulmonary hypertension. This complication is always accompanied by markedly reduced exercise tolerance and usually frank cyanosis.

PREDICTION OF PHYSIOLOGICAL COMPENSATIONS

Cardiovascular pathology produces changes in cardiac filling, ejection, and cardiopulmonary perfusion. The second step in our systematic approach is to predict the physiological compensations resulting from the abnormalities defined by the history, physical examination, and other evaluations. For instance, concentric ventricular hypertrophy is the normal compensatory response when ventricular ejection occurs against increased impedance (e.g., systemic hypertension, aortic stenosis, or tetralogy of Fallot). As a result of hypertrophy, adequate ventricular filling requires higher atrial pressure and is more dependent on atrial contraction than in the absence of hypertrophy. These abnormalities of ventricular filling are called "diastolic dysfunction," and they are very common in the elderly. Bradycardia is tolerated poorly in patients with diastolic dysfunction, because the ventricle does not dilate adequately to accommodate all the venous return causing a decrease in cardiac output.

Abnormalities in cardiac ejection are also predictable. The most common example is reduced ejection due to ischemia or infarction. However, other predictions require more thought. For instance, in severe aortic stenosis, left ventricular ejection is reduced but requires increased work and myocardial oxygen supply. When systemic vascular resistance falls, the work of this ventricle is maintained (because of the stenotic aortic valve), but its oxygen supply is decreased (due to lower aortic diastolic pressure). In contrast, in tetralogy of Fallot and idiopathic hypertrophic subaortic stenosis, the degree of ventricular outflow obstruction depends on the degree of ventricular filling and the vigor of contraction. Low preload and high contractility pronounce obstruction, while the converse relieve it.

Similarly, shunt physiology is predictable: the degree of shunting at the ventricular or great vessel level will depend on the size of the shunt and the relative resistances to flow in the pulmonary and systemic vasculature. For instance, an infant with hypoplastic left heart syndrome (large shunt at the great vessel level) will become hypotensive and acidotic if given too much supplemental oxygen (the oxygen lowers pulmonary vascular resistance and results in a "steal" of blood from the systemic circulation). In contrast, when an infant with a large ventricular septal defect (e.g., tetralogy of Fallot) becomes cyanotic, increasing systemic vascular resistance relieves the cyanosis by decreasing the right-to-left intraventricular shunting. Thus, when large shunts are present at the ventricular or great vessel level, the balance of pulmonary and systematic flows can be adjusted by changing the vascular resistances.

DETERMINATION OF HEMODYNAMIC GOALS

This is the third and most crucial step in our systematic process. In this step, we determine goals for the major hemodynamic variables affected by anesthesia: preload, heart rate, systemic vascular resistance, pulmonary vascular resistance, contractility, and rhythm. The goals for these variables depend on the cardiovascular pathology of the patient and are the direct consequences of the physiological compensations we predicted in the prior steps of this process. For instance, when ventricular filling is impaired because of hypertrophy, our goal is to maintain preload (high filling pressures), generous volume administration, and avoidance of factors that decrease venous return. Please note that the hemodynamic goals during anesthesia may be quite different than

*www.census.gov/ipc/www/usinterimproj/natprojtab02a.pdf.

the goals during chronic care of the patient. In the same patient with ventricular hypertrophy, a primary care physician may have spent months reducing preload ("pruning") to relieve symptoms of pulmonary congestion. However, this state of relative dehydration may be disastrous in some patients during induction of anesthesia.

Similarly, heart rate must be maintained at low normal levels in patients with dynamic ventricular outflow obstructions (tetralogy of Fallot and hypertrophic obstructive cardiomyopathy) to allow for adequate ventricular filling and ejection. Systemic vascular resistance should be reduced in patients with mitral regurgitation to promote forward ejection of blood, and maintained, or even augmented, in patients with aortic stenosis to provide adequate coronary artery blood flow. Pulmonary vascular resistance is difficult to lower in most patients without producing systemic hypotension. However, in patients with reactive pulmonary vasculature, it is not difficult to raise it. Hypercarbia, metabolic acidosis, hypoxia, and light anesthesia can result in dramatic increases in pulmonary vascular resistance. In the rare infant with too much pulmonary blood flow, one or more of these "therapies" may reverse hypotension and improve the systemic circulation.

In anesthesia dogma, too much emphasis has been placed on maintaining cardiac contractility. Indeed, the most successful cardiac drugs of our time have been myocardial depressants. Most patients tolerate modest decreases in contractility and some benefit: patients with coronary artery disease, hypertrophic obstructive cardiomyopathies, and tetralogy of Fallot. In contrast, no patient is improved by the loss of sinus rhythm, and some tolerate it quite poorly: patients with diastolic dysfunction who need their atrial "kick" to maintain an adequate stroke volume (i.e., aortic stenosis).

In each patient, some goals are more important than others, and this fact allows the clinician to prioritize management and interventions. For instance, a relatively slow heart rate (<80 bpm) and high systemic vascular resistance (greater than 1500 dynes/sec/cm^{-5}) are most important in patients with severe mitral stenosis. If such a patient is tachycardic, hypotensive, and overtly in congestive heart failure, the correct interventions may include a β blocker and a vasoconstrictor. Clearly, these interventions would be grossly inappropriate in many patients with congestive heart failure, but they will be effective in this patient, because they will restore the appropriate hemodynamic goals.

ANTICIPATING EMERGENCY TREATMENTS

This last step is really an extension of the prior one, but I list it separately to emphasize its importance. A few life-threatening hemodynamic changes recur often enough in patients with cardiovascular disease that they should be anticipated, and the treatment ready to execute. Examples would include severe hypotension following induction of anesthesia in patients with aortic stenosis, and severe cyanosis in patients with tetralogy of Fallot. Indeed, phenylephrine may be the drug of choice in both these emergencies, because the goal is the same—increased systemic vascular resistance. In a true crisis, the difference between effective management and chaos is anticipation and planning.

CASE EXAMPLES

Please consider the following case scenarios. In my lecture, I will outline my hemodynamic goals and anesthetic plan for these patients.

1. A 75-year-old male is scheduled for emergency laparatomy to relieve a small bowel obstruction. He has known of his heart murmur for more than 10 years and recently has noted dizziness during bowel movements. He is not physically active due to arthritis. He takes 5–10 aspirin a day. Examination reveals a 60 kg male in abdominal discomfort with BP 110/90, HR 90, and RR 20. He has severely reduced neck extension, diminished carotid pulsations, small mouth, systolic ejection murmur radiating to the neck, and a moderately distended abdomen. What are your hemodynamic goals and anesthetic plan?
2. A 3-year-old female is scheduled for emergency esophagoscopy to remove a penny from her upper esophagus. She has tetralogy of Fallot palliated with a right Blalock-Taussig shunt (subclavian to pulmonary artery). She becomes cyanotic when she cries and is scheduled to undergo complete correction of her cardiac defect in 3 months. She ate a full meal 1 hour prior to admission (including the penny). Examination reveals a 15-kg frightened female with BP 100/60, HR 100, RR 30, and sat 92%. She has a systolic ejection murmur heard throughout the precordium, and her fingers are mildly cyanotic and clubbed. What are your hemodynamic goals and anesthetic plan?
3. A 20-year-old female is scheduled for elective laparoscopic cholecystectomy. She has tricuspid atresia palliated by a series of operations culminating in a Fontan procedure at age 10. Her physical activity is limited to shopping and housework. Her medications include digoxin, diuretic, and ACE inhibitor. Examination reveals a 50-kg female in no distress with BP 90/70, HR 95, RR 20, and oxygen saturation of 92%. What are your hemodynamic goals and anesthetic plan?

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Controversy of Antifibrinolytic Agents in Cardiac Surgery

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LEARNING OBJECTIVES:

1. To review the evidence-based efficacy and safety of antifibrinolytic agents.
2. To discuss the meta-analysis of head-to-head comparison of antifibrinolytic agents.
3. To appraise the current options of antifibrinolytic use in cardiac surgery

BACKGROUND:

(Anesth Analg 2008;106:●●●–●●●)

Three antifibrinolytics have been routinely used during cardiac surgery, including aprotinin (AP), tranexamic acid (TA), and aminocaproic acid (EACA). When compared to placebo or inactive control, each of these antifibrinolytics has individually been shown to reduce blood loss in patients undergoing cardiac surgery. The number of published randomized placebo-controlled trials is greatest for aprotinin and least for aminocaproic acid, and it has been suggested that aprotinin should be the agent of choice since its evidence base is largest. In addition, aprotinin has been shown in some, but not all, meta-analyses, to reduce the risk of stroke when compared to placebo. However, the more important contemporary question is not whether aprotinin performs better than placebo, but whether it provides better outcomes relative to a comparable alternative–either tranexamic acid or aminocaproic acid. Given that over 1 million cardiac surgeries are performed worldwide and antifibrinolytics are used routinely during cardiac surgery in most centers, the need for clarity on this issue is urgent.

This debate has become particularly salient since the release of three publications related to two observational studies and one unpublished observational study comparing the risks of aprotinin with tranexamic acid or aminocaproic acid. The studies by Mangano et al. were based on a large surgical database derived from 69 institutions around the world, including 4374 patients. The studies raised safety concerns about aprotinin, in particular with respect to increased postoperative risk of renal dysfunction, myocardial infarction, heart failure, cerebrovascular events and increased 5-year mortality. A smaller, case-matched database study by Karkouti et al. in 898 high risk patients from a single institution also raised concerns of renal safety. After these studies triggered renewed FDA deliberations about the safety of aprotinin on September 2006, the FDA was informed by the Bayer Pharmaceutical of an additional unpublished observational safety study (i3 study, Schneeweiss et al.) involving close to 67,000 patients with preliminary results suggesting that, in addition to renal dysfunction, aprotinin may increase risk of death, congestive heart failure, and strokes. Other trials have not confirmed the increased risk of death, stroke, or myocardial infarction. These discrepancies may be due to power issues, differences in adjusting for confounders, and differences in comparators (active vs inactive control group). Warnings were issued from regulatory bodies in various countries emphasizing the need for judicious use of aprotinin with appropriate surveillance. Some experts suggested there was little need for change in practice, while others suggested that routine aprotinin use should be abandoned in favor of safer alternatives. Overall, the mixed messages have caused confusion, and objective clarification of the evidence is required before reasoned discussion can converge on evidence-based recommendations for practice.

A follow-up FDA public joint meeting of the Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee was held in September 12, 2007 to review the totality of evidence on the safety of aprotinin. FDA independently reanalyzed the data from the above studies by its Quantitative Safety and Pharmacoepidemiology group. The FDA concluded that the evidence for renal effect, including renal failure consistent; there is evidence for long-term mortality effect; but the effects for cardiovascular, cerebrovascular, and in-hospital death outcomes are not statistically demonstrated. The recommendations at that time were to keep the same safety warning as in September 12, 2006 of increasing risk of renal dysfunction and may increase the need for dialysis in the perioperative period after aprotinin use; indicated in cardiac surgical patients with increased risk of blood loss and blood transfusion; and the anaphylactic reaction with prior exposure; and of Bayer Pharmaceutical to perform randomized controlled trial on aprotinin to alteratives. However on October 19, 2007, FDA was informed of the Data Safety Monitoring Board's recommendation to stop patient enrollment in the Canadian BART study (a randomized controlled trial of the use of antifibrinolytics in high-risk cardiac surgical patients),

because of the consistent increased 30-day mortality in the aprotinin group in comparison to TA or EACA at the interim analysis near the completion of this study. On November 5, 2007, FDA requested market suspension of aprotinin, as one FDA officials was quoted, "F.D.A. could not identify a specific patient population where the benefits of using Trasylol could outweigh the risks." At the present time, the data of the BART study is being analyzed and pending submission for publication.

WHAT ARE THE BENEFITS AND RISKS OF AP VERSUS TA/EACA?

We recently performed a comprehensive meta-analysis of all available direct comparative trials. Bainbridge et al. (27 randomized and 2 observational comparative trials; 8590 patients) suggests that AP provides no proven clinical advantage over TA/EACA. The number of patients exposed to allogeneic RBC transfusion or any blood product transfusion is similar with AP or with TA/EACA when either randomized or nonrandomized trails are considered. When units of blood transfused is considered, at best, only modest reductions in total red blood cells administered were observed in the AP group versus TA/EACA (0.16 U/patient, ranging from a minimum of 0.07 U to maximum of 0.2 U per patient), which most clinicians would consider to be clinically insignificant. The results were also consistent across low-risk versus high-risk patient studies. On the other hand, the balance of the evidence suggests that, compared with TA/EACA, AP might cause harm including death, stroke, myocardial infarction, or renal dysfunction.

ARE THESE RESULTS BIASED?

While significant controversy remains regarding the validity of the current evidence base for quantifying the magnitude of risk of AP versus TA/EACA, it is important to put these risks into context. It is widely accepted that randomized trials represent the highest standard for determining treatment effects. However, the limitations of randomized trials in providing sufficient power to detect infrequent adverse events is also widely recognized and high quality observational trials have been embraced to fill gaps in the evidence where randomized trials fail to inform. Many randomized trials reported only bleeding and transfusion outcomes. The lack of statistical significance for estimates of harm does not prove lack of harm, but rather the wide confidence intervals show that the possibility of harm cannot be ruled out (insufficient data). Overall, even conservative interpretation of the totality of the evidence base directly comparing AP versus TA/EACA suggests that the results of randomized trials are compatible with nonrandomized trials.

IS OBSERVATIONAL DATA FATALLY FLAWED?

The controversy continues with the recent publications by Dietrich et al., Schneeweiss et al., and Shaw et al. In the current debate about the apparent discrepancy between randomized and observational comparative trials of aprotinin, the tendency has been to dismiss outright the observational data as fatally flawed. However, risk data from observational studies cannot be rightly dismissed simply on the basis of lack of randomization, as there is strong empirical evidence that observational studies more commonly estimate numerically smaller risks (i.e., more conservative numeric absolute and relative increases) than their corresponding randomized trials. Combining studies through meta-analysis may provide the ability to overcome some limitations of study size; however, randomized trials frequently enroll relatively low risk cohorts and underreport adverse events in their published reports. Observational trials allow the inclusion of a large cohort of patients with varying risk factors in the real world setting and thus may be better suited for studying adverse outcomes. While it is widely known that the best evidence for efficacy come from randomized trials, it is now accepted that the best evidence on harms will often come from large observational studies, particularly when the adverse events are uncommon or require long follow-up for detection.

WILL THE BART TRIAL END THE CONTROVERSY?

The BART trial, a randomized trial with a target sample size of close to 3000 high risk patients, recently halted enrollment because of safety concerns with aprotinin. Preliminary data from the BART trial suggest an increase in the mortality rate in the aprotinin-treated group compared to either the TA or EACA groups. The difference and the trend were not statistically significant but were concerning enough to terminate the trial before enrollment was complete. The lack of statistical significance should not be surprising given outcomes of a similar magnitude as those found in this meta-analysis; the sample size of BART was insufficient to demonstrate statistically significant differences in mortality for AP versus TA/EACA. BART was powered to find absolute differences in the range of 10% (from 50% to 40%) for blood transfusion and is not powered to rule out significant differences for risks in the range of 1% (as found in our meta-analysis).

WHAT ARE THE LIKELY ABSOLUTE DIFFERENCES IN BENEFITS AND RISKS?

If preliminary estimates are accurate in the BART study, for every 1000 patients treated with aprotinin instead of tranexamic acid, there would be an estimated: ~30 to 50 fewer massive bleeding events (including massive transfusion, re-operation for bleeding, or bleeding from chest tubes) [derived from published event rates of BART at interim analysis, and assuming an ARR = 3–5% for massive bleeding events for aprotinin versus tranexamic acid]. ~20 extra

deaths, even *after* the benefit due to reduced bleeding events and transfusions is accounted for [BART trial suggested NNH = 2%, which translates to 20 per 1000].

CONCLUSIONS AND IMPLICATIONS

The results of randomized and observational trials are congruent, and evidence to date shows no proven significant benefit of AP over TA/EACA. Patient exposure to blood transfusion is not reduced by AP when compared with TA/EACA, and the possibility that AP may cause harm including death, stroke, myocardial infarction, or renal failure cannot be ruled out compared with TA/EACA.

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Does Perioperative Glycemic Control Really Matter?

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OBJECTIVES: At the end of this session, the learner will

1. Understand the basis for current practices for managing glucose during the perioperative period
2. Interpret findings from recent studies on the benefits and risks associated with tight glycemic control in medical and surgical patients
3. Be able to develop an evidence-based plan for glycemic control in the perioperative period

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Glucose management has become an increasingly important aspect of perioperative care for both diabetic and nondiabetic patients. Recent literature has documented the frequency of hyperglycemia in the perioperative period and the morbidity and mortality associated with it.[1,2] Most clinicians now recognize that the blood glucose changes during surgery may be significant and a number of their management strategies may alter the blood glucose and therefore affect clinical outcomes. For example, the administration of steroids and other drugs increases blood sugar, sometimes for only short periods of time, and initiation of cardiopulmonary bypass and other intraoperative events alter glucose homeostasis. As a result, there has been more attention paid to the control of glucose, despite a lack of clarity as to how to address hyperglycemia, particularly in the nondiabetic patient, the specific goals for blood sugar levels and the most appropriate ways to both monitor and treat changes in glucose. As importantly, most anesthesiologists and critical care providers are concerned about hypoglycemia in the intraoperative period and its potential impact on postoperative course, particularly since many of the signs and symptoms of hypoglycemia are not apparent in the anesthetized or heavily sedated patient. This discussion will review the data on the risks of hyper and hypoglycemia in the perioperative period, the evidence to suggest that better glycemic control might improve outcomes and clarify whether the benefits of tight glucose control are sufficient to warrant greater attention to it in the perioperative period based on our current state of knowledge.

TRADITIONAL APPROACHES TO GLUCOSE CONTROL

The historic approach to management of blood glucose in the perioperative period is, for the most part, based on limited clinical investigation and anecdotal reports of the risks and benefits of a number of alternative strategies. In most cases, most anesthesiologists were trained to believe that patients with type I diabetes benefit from careful control of glucose in the perioperative period, while those patients with type II diabetes do not require intensive control. Most textbooks of anesthesia and critical care medicine that provide recommendations for glucose control for the diabetic patient emphasize the importance of careful monitoring of blood glucose levels with variable recommendations for insulin administration, usually based on the baseline insulin needs of the patient rather than a specific glucose management regimen based on serial blood glucose measurements. Many anesthesiologists were taught during their training to manage insulin-dependent diabetic patients by administration of 50% of their insulin dose the morning of surgery (as regular insulin, independent of the type of insulin usually administered) and thereafter to allow patients to resume the usual insulin regimen once oral feedings were initiated. More intensive insulin therapy was not recommended, in large part out of concern for the development of hypoglycemia which might be difficult to diagnose. In addition, the perceived complexity of monitoring glucose levels and implementing insulin therapy fostered an attitude of "therapeutic nialism." The basis for the recommendations described in most textbooks is unclear, but the folklore remained in both the literature and clinical practice.

Over the past few years, many studies have demonstrated that a more intensive management strategy may be appropriate and clinically indicated to optimize glucose control and minimize the complications associated with hyperglycemia. Most of the studies have been directed toward management of the patient either after surgery or optimal management of the patient with multisystem disease or other medical conditions during surgery, rather than for the "routine elective patient." Nonetheless, there are a number of studies that have documented the value of tight glucose control (generally designed to maintain serum glucose between 80 and 120 mg/dL) in a variety of surgical patient populations.[2–4] As a result of the outcomes from recent studies, the optimal approach to

monitoring and managing the patient who is undergoing anesthesia and surgery is undergoing refinement. As the debate about optimal management strategies continues and additional data are accumulated to help guide our management, it is critical for anesthesiologists to understand our current state of knowledge and develop a plan for managing hyperglycemia in the perioperative period.

IS PERIOPERATIVE HYPERGLYCEMIA A SIGNIFICANT PROBLEM?

Diabetes mellitus is a significant problem for an increasing percentage of the population. In addition, the complications of diabetes are a common cause for hospitalization and unfortunately increase the likelihood that a diabetic patient will require surgery and anesthesia. As many as 10% of adults in the United States have diabetes mellitus[5]; the percentage of the adult and pediatric population with diabetes is increasing due to a number of environmental and other causes. Diabetes contributes to overall morbidity and mortality; it is currently the sixth most common cause of death in the United States.[6] The risk of death for a diabetic patient is almost twice the risk for a matched cohort of nondiabetics.[6] The implications of this increased morbidity and mortality is magnified for the surgical patient population. Diabetics are estimated to represent at least 25% of hospitalized patients,[7] and are more likely than nondiabetics to undergo surgery. In diabetic patients undergoing elective surgery,[8] a blood glucose level >220 mg/dL is associated with an almost sixfold increase in nosocomial infections on the first postoperative day compared to those with lower glucose levels.

Hyperglycemia itself is a cause for increased morbidity and mortality; it is associated with sudden cardiac death, myocardial infarction, cerebral vascular accident, as well as worse outcome after ICU and hospital admission.[1,9–11] Hyperglycemia has also been shown to have other deleterious affects, including altered leukocyte function,[12] impaired wound healing, and a number of other complications. In both animal and human studies, hyperglycemia has been demonstrated to increase cytokine levels and cause an increased inflammatory.[3,12,13]

While hyperglycemia is associated with increased morbidity and mortality, it is probably not either recognized in most patients or its significance is underestimated. A number of studies have demonstrated that increases in blood glucose are remarkably common. It is seen in as many as 38% of hospitalized patients; while 26% of these patients have a prior history of diabetes, 12% have no history or findings to suggest diabetes.[2] In one study of hospitalized patients, hyperglycemia was identified in as many as 33% of surgical patients and 38% of medical patients. This group of patients had at least one serum glucose >200 mg/dL and 2/3 of these patients had two or more serum glucose levels >200 mg/dL.[14] These findings are not inconsequential. Newly discovered hyperglycemia has been associated with adverse outcomes including increased hospital mortality, longer length of stay, and a higher risk of infection.[1]

The perioperative management of patients also contributes to hyperglycemia and increased morbidity. For example, in a study of diabetic patients who underwent renal transplantation and received perioperative steroids, those with a higher mean blood sugar had a higher incidence of infection and acute rejection.[15,16] Recently a number of studies have evaluated the risks associated with hyperglycemia in a number of surgical patient populations. The most significant data have been generated for the patients undergoing cardiac surgery. In one group of patients, serum glucose >200 mg/dL within the first 48 hours after cardiac surgery was associated with twice the likelihood of surgical site wound infection.[17] Hyperglycemic events occurred commonly in this group of patients, even when they did not have a prior history of diabetes. In another study of diabetic patients, hyperglycemia within the first three postoperative days was an independent predictor of deep sternal wound infection, increased length of stay and death.[15]

IS THERE EVIDENCE TO SUPPORT THE NEED FOR TIGHT GLYCEMIC CONTROL?

Recognizing the risks associated with hyperglycemia in both diabetic and nondiabetic patients is important and interesting, but it begs the question as to whether controlling the hyperglycemia really matters. Since the management strategies in the perioperative period are challenging under the best of circumstances, the additional challenges associated with monitoring blood glucose and managing it if it is elevated make it critical to demonstrate that correcting hyperglycemic makes a difference in morbidity and mortality and that the benefits outweigh the risks. Many studies have been completed over the past few years that address this issue, some in surgical patients and some in more diverse critically ill patient populations. One of the earliest studies that documented the risk of hyperglycemia and benefit of tight glycemic control was reported by Van den Berghe, et al.[3] This prospective randomized trial demonstrated that hospital mortality rates were 37% lower in patients managed with tight glucose control than in controls. The authors also noted that there was a significantly reduced mortality in the subset of patients with no prior history of diabetes when their blood sugars were carefully controlled, once again demonstrating that hyperglycemia alone may be a significant risk factor for poor outcomes and that carefully managing is beneficial.[18]

Other studies of surgical patients have demonstrated reduced complications with strict control of the blood sugar. In one study that included 61 surgical

intensive care patients, tight control of the blood sugar between 80 and 120 mg/dL versus a control group whose blood sugar was between 18 and 200 mg/dL, resulted in reduced incidence of surgical site, bloodstream, and intravascular device-associated infections. Similarly, in the study by Furnary and others, the increased incidence of wound infection and other complications was reduced with implementation of a continuous insulin infusion titrated to reduce the blood glucose.[15]

Unfortunately, interpretation of the studies is challenging, since the beneficial findings related to blood glucose control are not consistent in all studies. In a study that included patients undergoing cardiac surgery, no difference in outcome was identified whether the blood glucose was maintained between 80 to 110 mg/dL or was allowed to remain >200 mg/dL.[19] Patients in both groups were treated with insulin infusions to achieve the desired end-points in this study, one group tightly controlled and the other not. The most noteworthy finding of this study is that there were more deaths and strokes in the in the intensive insulin therapy group after surgery, although the investigators could not identify any difference in length of ICU or hospital length of stay.

While there may be contradictory data for surgical patients, the benefits of tight glucose control in medical ICU patients may be even less obvious. Van den Berghe and colleagues did a follow-up study to their initial investigation in which they instituted an insulin infusion in 1200 medical ICU patients to maintain serum glucose levels between 80 and 100 mg/dL (although they did not consistently achieve their goal in the study population).[2] In this study, the use of the insulin infusion significantly reduced morbidity, but not mortality except in the subpopulation of patients with an ICU length of stay <3 days. Perhaps most importantly, the study group had a higher incidence of hypoglycemia a complication that may be associated with serious sequelae, in some cases of more concern than those related to moderate hyperglycemia.

Subsequent to this second study, Van den Berghe and colleagues analyzed data for over 2700 patients enrolled in both randomized controlled trials in the ICU.[18] This study provided additional evidence of the risks of hypoglycemia associated with tight glycemic control, although the findings are somewhat different. The study demonstrated that in this population of ICU patients, intensive insulin therapy reduced mortality without regard to ICU length of stay. Hypoglycemia was more common in the patients intensively treated, although ironically, death within 24 hours after a hypoglycemic episode was more frequent in the control (conventionally treated) group. Following a hypoglycemic episode, there was no increase in neurological sequelae or long-term mortality.

The incidence of hypoglycemia is of great significance to the surgical patient, both in the operating room and ICU. First, hypoglycemic is difficult to diagnose clinically in the anesthetized or heavily sedated patient. Second, even with frequent measurements of blood glucose, the Van den Berghe studies and others have demonstrated a high rate of hypoglycemia. In one recent study of patients in a medical-surgical ICU, a number of risk factors associated with hypoglycemia were identified.[20] Risk factors that were independent predictors of hypoglycemic episodes included a decrease in the rate of nutritional supplementation with the same insulin infusion rate, use of bicarbonate substitution fluids during hemofiltration, preexisting diabetes, sepsis, and inotropic support.[21,22] While these specific risk factors may not be significant for the surgical patient in the operating room, they are important considerations in the perioperative care of patients at risk.

The concerns about hypoglycemia have become the emphasis of recent studies and, in fact have recently resulted in suspension of a number of large multicenter trials. The VISEP trial comparing conventional versus intensive insulin therapy in septic medical and surgical patients was halted following enrollment of 488 patients with severe sepsis because of frequent hypoglycemic episodes associated with intensive insulin therapy and no difference in mortality.[23] Similarly, the Gluconotrol trial in Europe was suspended after enrolling 1100 patients due to a high rate of hypoglycemia (glucose <40 mg/dL) and higher mortality in the tight glucose control group.[24] In that study, the goals for the tight glycemic control was a glucose between 80 and 110 mg/dL compared with a "control" group whose glucose was maintained between 140 and 180 mg/dL.

Other studies have continued to evaluate the value of tight glycemic control on outcomes including but not limited to hypoglycemia. The NICE-SUGAR (Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) study being performed under the auspices of the Australian and New Zealand Intensive Care Society and the Canadian Critical Care trial group is assessing the outcomes for 6000 medical and surgical ICU patients with either intensive insulin therapy to maintain blood glucose levels between 80 and 110 mg/dL versus a control group whose blood glucose is between 140 and 180 mg/dL mg/dL.[25] The outcome of this study will provide additional information about the importance of tight glycemic control. In the past month, however, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) Trial was suspended due to a high frequency of complications associated with tight glycemic control, including increased risk of heart attack and stroke.[26]

THE CHALLENGES ASSOCIATED WITH MONITORING BLOOD GLUCOSE

Tight glycemic control requires frequent–and accurate–monitoring of serum glucose with devices. One of the

primary reasons for the increasing interest in managing and optimizing the blood glucose is because we now have technologies available to us to monitor blood glucose at the bedside and to titrate insulin infusions relatively easily.

These technological advances allow us to monitor blood glucose regularly, usually with a point-of-care device that measures venous or capillary samples. Some invasive continuous devices have also been evaluated and demonstrate good correlation with arterial samples.[27] Other devices such as the GlucoTec provide glucose management algorithms that also automatic adjustments in insulin infusion rates to improve tight glycemic control. As the technology advances, these biofeedback devices will facilitate glucose management and should reduce the risks associated with major fluctuations in serum glucose.

Since most anesthesiologists do not use advanced algorithms or monitoring systems to manage the patient in the operating room, it is critical to understand the limitations of some of the bedside devices and ensure that the measured glucose level is correct. While a number of technologies are available to monitor blood glucose levels, the results from point-of-care devices and other bedside monitors vary from the results of blood glucose samples sent to a central laboratory. In one study evaluating a bedside glucometer used in the ICU, a significant error rate was found in patients with anemia. As the hematocrit fell, the measured blood glucose was erroneously high compared with those reported by the reference laboratory. These investigators were able to develop algorithms ("correction factors") specific to each bedside device as a way to "predict" the blood glucose that would be reported by the central laboratory.[14,28] Another study demonstrated significant differences in the blood glucose measured from capillary versus arterial samples, with capillary samples consistently overestimating the serum glucose.[29] In this study, all measurements from the bedside glucose monitor were higher than samples analyzed in the central laboratory. Since hypoglycemia has serious consequences, the problems associated with underdiagnosing low blood glucose levels are significant. These studies demonstrate the importance of calibrating the bedside monitor to the reference laboratory so that significant hypo- or hyperglycemia is not missed. Most importantly, if tight glycemic control is the goal of management, each clinician must be trained to use the monitoring device correctly, validate quality control measures, and understand the limitations of the technology in order to interpret the laboratory data correctly and manage the patient appropriately.

HOW DO WE OPTIMIZE CARE OF THE PATIENT IN THE PERIOPERATIVE PERIOD?

On the basis of the findings from the most recent studies, the anesthesiologist and critical care practitioners must decide how best to monitor and manage the blood glucose. For the anesthetized patient, and in some respects similarly for the critically ill patient in the ICU, the ultimate goal may be to control hyperglycemia, while avoiding the risks associated with even short periods of hypoglycemia. In the anesthetized patient, however, the goals may require some modification, since the signs and symptoms of hypoglycemia may be masked. Without careful (continuous?) monitoring of blood glucose, moderate hyperglycemia will be acceptable in order to avoid hypoglycemia. The outstanding and unanswered question is whether moderate hyperglycemia, whether transient or sustained, carries with it increased risks that outweigh those associated with mild hypoglycemia.

Another barrier to tight glycemic control in the operating room setting is the perception that frequent monitoring of blood glucose is burdensome and distracting from other responsibilities, just as it has been identified as labor intensive by the ICU nurse. Whether these reasons are sufficient to justify maintaining blood glucose above "normal" requires further investigation. In the meantime, some recent studies have documented the challenges associated with the monitoring requirements associated with tight glucose control, particularly in the unstable patient and question the level of glucose that requires treatment. Despite these concerns, the studies have identified a number of potential benefits to "controlling" the blood glucose, minimizing wide variability and managing insulin therapy to keep the glucose within a reasonable range, generally between 80 and 120 mg/dL. More tight control may be desirable, but with the current level of technology for monitoring glucose levels and the current infusion methods available to us, it may be difficult to accomplish. As the technology for both monitoring and treatment become available, the goals for management will change.

A number of issues have yet to be satisfactorily resolved. First, we have to determine the optimal target for blood glucose and whether it is the same for every patient population. The evidence is conflicting, with benefits associated with tight glucose control in certain populations, and the risks outweighing the benefits in others. Second, the currently available methods for managing glucose add complexity, particularly during a challenging and unstable operative procedure or in the hemodynamically unstable ICU patient. While intermittent administration of subcutaneous or IV insulin is thought to be straightforward, the initiation and management of an insulin or insulin-dextrose infusion has not been commonplace in the operating room and is therefore not considered a routine way to manage blood glucose. On the other hand, the use of insulin infusions has been demonstrated to improve glucose control and, in many cases minimize (though not eliminate) the risk of hypoglycemia. As algorithms and feedback mechanisms become available to monitor the blood glucose and automatically adjust insulin and glucose infusions become available, tight glucose control in appropriate

patient populations will become the standard of care. In the meantime, the anesthesiologist must weigh the risks and benefits in each patient to determine how best to manage glucose and how tightly to control the range of variability. Third, not only do we need additional studies to validate which populations will benefit most from tight glucose control, but we also need better data to define the actual range for serum glucose. Most studies have had goals for serum glucose between 80 and 110 or 120 mg/dL. However, it is difficult, and may be impossible, to determine if benefits are gained with any level of control of hyperglycemia or the level of glucose that may be acceptable to minimize the likelihood of any hypoglycemic episodes. Finally, additional studies, some currently underway, are needed to evaluate whether the risks of sustained moderate hyperglycemia are greater or less than the risks associated with marked "glycemic variability" with large swings in blood glucose that may be associated with other risks we have yet to quantify.

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Red Blood Cell-Nitric Oxide Interactions in Health and Disease: Overview

Steven A. Deem, MD

The interactions between red blood cells (RBCs) and nitric oxide (NO) play complex and important roles in the regulation of blood flow in the systemic and pulmonary circulations. At the simplest level, RBCs inactivate NO through hemoglobin-oxidation, an interaction that promotes vasoconstriction in the lung during hypoxia (hypoxic pulmonary vasoconstriction) and in the periphery during normoxia. RBCs also promote production of NO through shear-stress interactions with the vascular endothelium and via hemoglobin-mediated reduction of nitrite. This lecture will review RBC-NO interactions in the context of health and disease, and discuss the therapeutic potential of this relationship.

Peripheral Nerve Blocks for Ambulatory Surgery: It's the Present and the Future–Catch a Quality Wave

F. Kayser Enneking, MD

OBJECTIVES: This lecture will review the rationalization for the use of peripheral nerve blocks in an ambulatory setting. In addition, the quality-of-care implications for the use of peripheral nerve blocks, both advantages and disadvantages, will be discussed.

(Anesth Analg 2008;106:●●●–●●●)

Ambulatory surgery presents many unique and conflicting challenges for anesthesiologist's in the year 2008. While there is an ever-growing demand for greater efficiency and access by administrators and surgeons, there is an equal demand for providing care for increasingly ill patients undergoing more complex surgery on an outpatient basis. Mixed in this brew is the appropriate demand for high-quality care and the development of quality of care-outcomes measurements. This paper will review the role of the routine application of peripheral nerve block (PNB) techniques in the quality outcomes for ambulatory surgery.

DEFINING QUALITY IN OUTPATIENT SURGERY

Outpatient surgery, whether performed in a hospital or ambulatory surgery center, has a common goal; pain-free, nausea-free, and complication-free patients who leave the facility within a reasonable span of time on the day of surgery.[1–4] Thus quality measures for outpatient surgery should reasonably examine patient's rating of pain control, incidence of nausea, length of stay in the facility, and unplanned hospital admission rate. Complications that arise after discharge from the facility, including poorly controlled pain and return for further care, are increasingly recognized as important factors in quality care and patient satisfaction.[3]

THE ROLE OF PNB IN QUALITY FOR OUTPATIENT SURGERY

Pain is the one of the common and distressing complications after ambulatory surgery.[5–8] Over 30% of patients' rate pain on a verbal rating scale as greater than 4 out 10 during the first 24 hours following ambulatory surgery.[8] However, in selected populations, the proportion of patients complaining of moderate to severe pain is even higher.[7] Poor pain control is the harbinger for poor outcomes in ambulatory procedures. Poor pain control is associated with increased use of opioid analgesics and in the incidence of nausea and vomiting. Difficulty with pain management leads to prolonged facility recovery times, increases in unplanned hospital admission, and return to the hospital encounters. As such, the move to multimodal analgesia has been led by the ambulatory surgery community, and the routine use of PNB for these patients plays a prominent role in ambulatory analgesia.

Chung et al. studied over 10,000 patients and reported that severe pain in the post-anesthesia care unit (PACU) was highest among patients undergoing orthopedic surgery.[6] Other studies have shown high pain scores for patients undergoing breast surgery and inguinal hernia repair.[7] Each of these groups of patients has associated PNB techniques that can be used to effectively reduce postoperative pain scores.

In a randomized controlled trial of patients undergoing hand surgery, McCartney et al. demonstrated significantly decreased pain scores in the PACU for patients receiving axillary plexus block compared to general anesthesia (GA).[9] The decrease in pain led to decreased opioid use and nausea, and shorter discharge times. Hadzic et al. demonstrated remarkably similar findings when comparing infraclavicular brachial plexus block to GA for minor hand surgery.[10] A meta-analysis that included both of these studies reported a decrease in PACU visual analog scores (VAS) for pain from 35.8 mm (out of 100) to 9.6 mm comparing PNB to GA for a variety of predominantly orthopedic ambulatory procedures.[11]

These findings are not entirely unexpected in upper extremity surgery, where it is possible to anesthetize the entire operative extremity with a single injection, using widely taught techniques, and avoiding GA. Interestingly, these same benefits can be seen when a femoral nerve block alone is used in combination with a GA for patients undergoing knee surgery.[12] This block often misses the obturator nerve and always misses the sciatic innervation of the knee yet its application decreases the narcotic requirements to such an extent that benefits are easily accrued.

For truncal surgery, most commonly breast surgery and inguinal hernia repair, paravertebral block (PVB) at the appropriate levels provides dense intraoperative anesthesia, decreased PACU pain scores, and

prolonged postoperative analgesia.[13–15] Other techniques of local anesthetic application are also effective. Ilioinguinal-iliohypogastric field blocks combined with heavy sedation have also demonstrated the usual triad of decreased pain scores, narcotic usage, and time to discharge compared with either spinal anesthesia or GA in a randomized study of 81 outpatients.[16] However, when ilioinguinal field block was compared with lumbar PVB for pediatric hernia repair, the lumbar PVB was associated with decreased pain scores, leading to less opioid consumption and increased surgeon and parent satisfaction levels.[17] Either technique, PVB or local field block, appears to improve outcomes compared to no block for these patients.

ISSUES WITH PNB IN OUTPATIENT SURGERY

Seemingly, PNB offers the ideal mechanism for providing analgesia in the ambulatory setting. The limitations to its use have traditionally included associated complications, surgeon acceptance, and time constraints for busy practitioners.

Some of the risks associated with PNB can be generalized, such as local anesthetic toxicity. Other risks are more specific to individual blocks such as shortness of breath associated with interscalene block (ISB) or falls after lower extremity block. One of the most commonly cited risks with PNB is nerve injury. Brull et al. have provided a review of contemporary estimates of risk of nerve injury with PNB.[18] Although the analysis consisted of mostly retrospectively self-reported cases series, their findings are encouraging. Overall, the investigators estimated the risk of neuropraxia after PNB to be 3% with resolution within 12 weeks for the vast majority of reported cases. In addition, it should be noted that ". . . Among the 16 studies in which complications were sought 12 months after PNB, only one case of permanent neuropathy was reported."[18] This estimate of low rate of permanent injury is tangentially verified by the ASA Closed Claims Data Base.[19] In the data base from 1980 to 1999, there are <20 high-severity (permanent/disabling or death) injuries associated with PNB, excluding ocular blocks. These claims were associated not only with nerve injury, but also with local anesthetic toxicity and inadequate monitoring of sedation. Although all the usual caveats regarding the closed claims database apply, it is clear that PNB has a wide safety margin.

Despite this impressive reported safety record with PNB, specific risks are worth reviewing. ISB block for shoulder surgery is an essential component of analgesia for this most painful outpatient surgery.[6] Brull et al. found the risk of neuropathy associated with ISB to be higher than for any other PNB in their report.[18] Borgeat and colleagues looked specifically at risk of nerve injuries following ISB in 520 patients who received both single-shot and continuous techniques.[20] They reported an astonishing rate of 14% neurapraxia within the first weeks after surgery. All but one of these patients had resolution of their symptoms within 9 months. Stretch injury, postoperative splinting, and preexisting subclinical neuropathy of the brachial plexus rather than direct needle trauma were deemed likely contributors to this high rate. Meticulous care in positioning and documentation of preexisting neuropathy is warranted in this patient population specifically.

Another specific risk of PNB is the risk of falling after lower extremity block. The reported incidence of this complication is low but probably widely underdocumented.[21] After reporting three falls following femoral block, Muraskin et al. undertook a volunteer study of stability after lower extremity block. Turning and pivoting appear to be high-risk maneuvers in patients after lower extremity PNB, particularly if immobilizing braces are not used. This finding in volunteers needs to be confirmed in a patient population. But the use of knee-immobilizing devices has been shown to reduce the number of falls in patients with femoral neuropathy.[22] The use of immobilizing braces and patient education seem to be reasonable steps to reduce risk of falling in patients who have received lower extremity PNB.

Surgeon acceptance or, more commonly, disinterest in the use of regional anesthesia for their patients has always had wide geographical variation. A recent survey of 468 Canadian orthopedic surgeons found that nearly half of all surgeons "directed" their patients' choice of anesthetic and that 80% of those surgeons directed their patients to choose regional anesthesia (RA).[23] Reasons cited favoring RA included less postoperative pain (32% of all responders), decreased nausea and vomiting, and safety. Reasons cited for not favoring RA for their patients included delays in the induction of anesthesia (43% of all responders) and unpredictable results. The use of an out of operating room block area has been shown to reduce OR anesthesia controlled time both in inpatient and outpatient surgery.[24,25] For busy ambulatory practices, establishing a block area clearly improves efficiency.[26] For surgeon satisfaction and their active promotion of the technique, the use of a block room is essential.

The overall success rate for PNB improved with the advent of routine nerve stimulator use for guidance during block performance compared with techniques incorporating paresthesias or fascial clicks. Still, the overall success rate is probably 85%–95% in experienced hands.[27] Use of ultrasound technologies may indeed improve on that overall success rate and improve efficiency of PNB techniques in the ensuing years.[28]

THE REAL CHALLENGE FOR PNB IN OUTPATIENT SURGERY

As discussed above, PNB techniques lead to favorable outcomes following ambulatory surgery. The real issue for me is that single injection PNBs have a finite resolution time in the postoperative period, generally

after the patient has been discharged from the ambulatory facility. In some patients, all the benefits of the PNB are predictably lost with the resolution of the block. Factors that lead to severe pain after block resolution include the magnitude of the operation, the lack of following postoperative analgesic regimens, and hyperalgesia from chronic opioid therapy. In a short communication regarding ambulatory shoulder patients, Wilson et al. found the mean length of ISB to be 22.5 hours.[29] On a 6-point scale (0–5) two thirds of patients reported a score of 3 or higher during the postoperative period after ISB resolution.

The obvious answer to this clinical problem is the introduction of continuous PNB (cPNB) for pain control following ambulatory surgery. The benefits of cPNB in outpatients have been widely documented.[30–35] Few serious complications have been reported in the literature, and the risk/benefit ratio for use in outpatients appears robust. The most difficult issue facing practitioners is the reasonable application of these techniques, which are labor intensive and expensive. As an example, the patients undergoing outpatient shoulder surgery in the report of Wilson et al. had undergone a variety of shoulder procedures.[29] There was no common procedure that induced more pain compared with other shoulder procedures. Two thirds of these patients reported severe to moderate pain, yet only one of the four patients undergoing open shoulder surgery (widely acknowledged to be more painful than arthroscopic surgery) complained of moderate to severe pain. The conundrum of wise application of this more expensive and laborious technique is a challenge for all ambulatory anesthesiologists.

FUTURE CHALLENGES FOR PNB IN OUTPATIENT SURGERY

The future is now. The drum beats of high-quality care and greater efficiency in the delivery of that care are loud and clear. The most common etiology for an outpatient failure (unanticipated hospital admission, return for care, or prolonged postoperative recovery) is pain. The ability to provide analgesia throughout the perioperative period is a shared responsibility. A concerted team effort is required to establish appropriate benchmarks for pain control. The wealth of information regarding the benefits of PNB in the ambulatory surgery population is welcome and should provide impetus for these modalities to be employed more universally. Our next challenges are in extending the duration of these techniques through novel local anesthetic formulations and delivery systems, through enhanced multimodal regimens, and through appropriate patient selection for out-of-hospital care.

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Myofascial Pain: Current Concepts

F. Michael Ferrante, MD

REGIONAL MYOFASCIAL PAIN SYNDROME

Myofascial pain is a muscular syndrome that is regional in nature, i.e., localized to particular sets of functional muscle groups in a particular region of the body. Classically, myofascial pain is observationally defined by the presence of trigger points in the bellies of muscles. Trigger points are palpable, hypersensitive, taut bands that generate twitch and referred pain upon palpation. The referred pain must, at least in part, replicate the patient's pain complaint. Trigger points come in two varieties. "Active" trigger points are painful both at rest and with activity. "Latent" trigger points are painful only when palpated. "Taut bands" are palpable rope-like hardening of a group of tense muscle fibers that may possibly contain a myofascial trigger point. Characteristics of involved muscles include: (a) chronic stiffness, (b) palpable hard or spasmodic texture, (c) easy fatigability (muscular not systemic fatigue), and (d) an association with headache (chronic tension type headache or migraine). Myofascial pain syndrome is quite common with a higher prevalence in women than men (2:1), and its prevalence increases with age.[1–3]

Several pathophysiologic mechanisms have been proposed for the development of myofascial pain: (a) sustained muscle overload or repetitive strain cause fatigue, local ischemia, and chronic release of algesic peptides after injury; (b) an abnormality of the neuromuscular junction for recovery of calcium with resultant energy deficit causes a lower activation threshold at the neuromuscular junction; (c) dysfunctional biomechanical relationships among functional muscle groups result in deconditioning, atrophic changes, and functional loss; and (d) peripheral or central sensitization. These mechanisms attempt to define myofascial pain as a primary muscle pathologic process (mechanisms 1 through 3, and they may be interrelated) or merely a secondary muscular manifestation of another pathologic process occurring elsewhere (mechanism 4). The common etiologic thread among all the proposed mechanisms is that myofascial pain is directly and causally related to soft tissue injury or secondarily related to biomechanical adaptation to injury.

FIBROMYALGIA

In contrast, fibromyalgia[4] is a systemic disease that is also observationally defined. Fibromyalgia is defined by the presence of tender points. Tender points are discreet areas of focal muscle tenderness that are elicited upon palpation and are localized over muscle, bone, tendon, and fat. The tender points are found at muscle-tendon junctions and characteristically do not reside in muscle bellies, as do trigger points. Palpation of tender points does not cause referred pain. Patients with fibromyalgia may also have trigger points. The American College of Rheumatologists has published diagnostic criteria for establishing the diagnosis that include chronic widespread pain for greater than 3 months with mechanical allodynia in at least 11 of 18 tender points in defined anatomic locations. Similar to myofascial pain, there is a higher prevalence in women than men (although the female to male predominance is 10:1 in. fibromyalgia). Comorbid conditions in fibromyalgia include sleep disturbances, neuroendocrine abnormalities, and immune system dysfunction, consistent with the systemic nature of the disease. Table 1 outlines T1
the distinctive characteristics of regional myofascial pain and fibromyalgia. The rest of the discussion will focus only on regional myofascial pain.

EVALUATION OF BIOMECHANICAL ABNORMALITIES

When chronically present, trigger points do not occur in isolation but are rather the result of an interplay of etiologic factors. It is almost the lore of the anesthesiologist that "dry" needling[5] or injection[6] should have a long-term, i.e., curative, rather than palliative effect. Such a conceptualization may be too simplistic and may ignore the presence of biomechanical muscular relationships that may generate and perpetuate myofascial pain. The evaluation and treatment of myofascial pain syndrome should not merely denote trigger points and their location for injection but rather direct therapeutic maneuvers towards normalization of posture and biomechanics.[7]

Correct posture and normality of biomechanical relationships is most easily assessed by examination of an anatomic "plumb line" extending from the tragus of the ear, to the coracoid process of the shoulder, to the greater trochanteric of the femur, to the lateral malleolus of the ankle. Any deviation from this "plumb line" can potentially generate a myofascial pain syndrome as biomechanical relationships among functional muscle groups are altered.

When patients present with myofascial pain syndrome of the shoulders and the neck, measurement of the tragus-coracoid line should always be performed.

Table 1. Differences Between Myofascial Pain and Fibromyalgia

	Myofascial pain	Fibromyalgia
Gender (female:male)	2:1	10:1
Defined by trigger points	(+)	(−)
Defined by tender points	(−)	(+)
Localization	Muscle belly	Muscle-tendon junction
Distribution	Regional	Widespread
Systemic fatigue	(−)	(+)
Neuroendocrine abnormalities	(−)	(+)
Sleep disturbance	(−)	(+)

Notation should be made of the presence of the tragus forward of the coracoid or *vice versa* (and measured simply in fingerbreadths). Patients with "rounding of the shoulders" will present with deviation of the tragus-coracoid line with the coracoid forward, suggesting weakening of muscles responsible for scapular stabilization. The weakening of the scapular stabilizer muscles (rhomboids, lower trapezius, infraspinatus, and supraspinatus) with shortening of the pectoral muscles causes internal rotation of the shoulder girdles. On the other hand, patients can develop a forward head posture, sometimes referred to as "propulsion" or "forward head syndrome." Forward head syndrome is quite common in patients with myofascial pain of the shoulders and the neck. Cervical paraspinal muscles are shortened and cervical protraction and capital extension occurs. The upper trapezius muscles and levator scapulae muscles are elevated and shortened. The pectoral muscles are shortened and painful. Scapular stabilization issues and propulsion commonly occur together in the same patient. It is simplistic to think that trigger point injections themselves may have long-term therapeutic benefits unless underlying biomechanical relationships are addressed and normalized.

POSSIBLE RELATION OF CERVICOTHORACIC MYOFASCIAL PAIN TO SPASMODIC TORTICOLLIS (OR CERVICAL DYSTONIA)

For the purposes of our discussion the terms "spasmodic torticollis" or "cervical dystonia" will represent the same disease process and be used interchangeably. Regardless of etiology, cervical dystonia is a syndrome of sustained involuntary neck muscle contractions quite often associated with painful muscles causing: (a) abnormal head or shoulder posture, (b) disturbed voluntary control of head movement, and (c) involuntary movements. Pain from continuous muscle contractions, cervical radiculopathy, cervical spondylosis, cervical facet arthropathy, and mechanical traction on musculoskeletal structures including ligaments and muscles is often associated with spasmodic torticollis. The prevalence of trigger points in spasmodic torticollis is unknown.

Table 2. Clinical Overlap Features

Variable	Spasmodic torticollis	Myofascial pain
Abnormal Posture	(+)	(+)
Limitation in range of motion	(+)	(+)
Pain: "aching," "pulling," "burning" and "tightness"	(+)	(+)
Hypertrophy of muscle	(+)	(?)
Trigger points	?	(+)
Tender points and taut bands	(+)	(+)

Is it possible that certain patients with myofascial pain may have characteristics that ostensibly (and perhaps not pathophysiologically) "overlap" with spasmodic torticollis? As mentioned previously, myofascial pain of the head and neck can be associated with abnormal head or shoulder posture, meeting one of the potential criteria for diagnosis of cervical dystonia. The most common qualities of pain described in patients with cervical dystonia[8] include "aching" (48.3%), "pulling" (34.3%), and "burning " and "tightness" (9.4% each), reminiscent of the descriptors used in myofascial pain. The incidence of arm pain (potentially indicative of radiculopathy) in patients with spasmodic torticollis was 14.7% according to the study of Tarsy and First.[8] There is a high incidence of pain referred to the hand in patients with cervical myofascial syndrome. (Myofascial pain defies dermatomal anatomic boundaries found with radiculopathies and characteristically refers to all the digits of the hand.) According to the study by Galvez-Jiminez et al., localization of headache in cervical dystonia was: frontal region (43%), temporalis muscle area (68%), occiput (61%), cervical region (71%), and shoulder (18%).[9] The percentages and localization of headache are very reminiscent of the prevalence and location of headache in patients with cervical myofascial pain.

Thus, there is much circumstantial evidence to suggest an overlap of clinical characteristics between patients with spasmodic torticollis and certain forms of cervicothoracic myofascial pain. These findings are summarized in Table 2. If the injection of botulinum toxin is T2
effective in the treatment of cervical dystonia, might this suggest potential efficacy in patients with cervicothoracic myofascial pain and a postural abnormality?

TREATMENT OPTIONS FOR MYOFASCIAL PAIN

Traditional therapies for the treatment of myofascial pain have included pharmacotherapy (nonsteroidal antiinflammatory drugs, steroids, tricyclic antidepressants, vasodilators, oral skeletal muscle relaxants), injection therapy ("dry" needling or trigger point injection of local anesthetic with and without corticosteroid), physical therapy, and behavioral modification. Such traditional therapies result in long-term benefit that is transient, variable, often incomplete, or nonexistent.[10,11]

ANOTHER OPTION: INJECTION OF BOTULINUM TOXINS?

Botulinum neurotoxin is produced by the spore-forming bacterium *Clostridium botulinum*. There are seven distinct serotypes of the neurotoxin (A, B, C1, D, E, F, G). Serotype A is the most potent. Botulinum toxin has a molecular weight of approximately 150,000 Daltons and is a dichain polypeptide. The 100,000-Dalton heavy chain (allows internalization of the light chain) is linked by a disulfide bond to the 50,000-Dalton light chain. A number of SNARE proteins (synaptobrevin, SNAP-25, and Syntaxin) allow synaptic vesicles containing acetylcholine to bind to pre-synaptic membranes and fuse, releasing neurotransmitter into the synaptic cleft. Different toxin serotypes bind to distinct SNARE proteins and have unique cleavage sights. Cleavage of the SNARE protein prevents binding of vesicles containing acetylcholine with the pre-synaptic membrane, thereby blocking acetylcholine release at the neuromuscular junction. The light chain of botulinum toxin serotype A binds to SNAP-25, while the light chain of botulinum serotype B binds to synaptobrevin.[12]

Botulinum toxin serotype A has been shown to inhibit the release of a number of nociceptive neurotransmitter peptides via an identical SNAP-25 cleavage mechanism, preventing fusion of synaptic vesicles to the pre-synaptic membrane. These peripheral peptides include glutamate, substance P, and calcitonin gene-related peptide.[13,14] Moreover, botulinum toxin has been shown to have an antinociceptive effect by inhibition of peripheral and central sensitization.[15] Thus, any potential analgesic effects from botulinum toxin in the treatment of myofascial pain could result from chemodenervation (muscle relaxation) and antinociception.

There are currently two commercial preparations of botulinum toxin available in the United States for clinical use: botulinum toxin type A (BOTOX®; Allergan, Inc.) and botulinum toxin type B (Myobloc®; Solstice Pharmaceuticals). (A third preparation [another serotype A] is anticipating entry to the U.S. marketplace.) Botulinum toxin is currently approved in the United States for treating cervical dystonia, strabismus, laryngeal spasm associated with dystonia, and glabelar lines.

PREVIOUS STUDIES

The literature is contradictory with respect to the efficacy of botulinum toxin in the treatment of myofascial pain. Early studies were powered with too small a number of patients to be deemed more than probes.[16,17] Alo et al.[18] and Lang[10] performed uncontrolled open-label studies, which did suggest efficacy. Freund and Schwartz performed a double-blind, randomized, placebo-controlled trial of direct trigger point injection in patients with chronic whiplash injuries, showing reduction in pain and improved cervical range of motion.[19] Wheeler et al. performed two double-blind, randomized, placebo-controlled trials of direct trigger point injection without positive results.[11,20] Ferrante et al.[7] using a double-blind, randomized, placebo-controlled design demonstrated that direct injection of botulinum toxin into trigger points was ineffective in the treatment of cervicothoracic myofascial pain.

CONCLUSION

Could botulinum toxin be effectively used to treat myofascial pain? Previous studies suffered from a number of problems with methodology. Future studies must address the effects of dosing, volume, postural abnormalities, choice of muscles to inject, injection site, and injection technique.

Still, there appears to be accumulating evidence that patients with cervical myofascial pain, headache, and cervical dystonia may have common clinical features. The use of botulinum toxin in patients with cervical myofascial pain should be limited to those individuals with overlap features of spasmodic torticollis and must be coupled with aggressive rehabilitation to restore biomechanical abnormalities.

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Consensus Panel Recommendations for the Management of Postoperative Nausea and Vomiting

Tong J. Gan, MB, FRCA

Postoperative nausea and vomiting (PONV) are two of the most common and unpleasant side effects following anesthesia and surgery. In the United States, more than 71 million inpatient and outpatient operative procedures are performed each year.[1] Untreated, PONV occurs in 20% to 30% of the general surgical population and in up to 70% to 80% of high-risk surgical patients.[2–4] The adverse effects of PONV range from patient-related distress to morbidity. PONV associated with ambulatory surgery increases health care costs due to unanticipated hospital admission, and accounts for 0.1% to 0.2% of these unanticipated admissions, which is significant in the United States where more than 31 million patients undergo ambulatory surgery each year.[1,5–7] It is estimated that an episode of vomiting prolongs post-anesthesia care unit (PACU) stay by about 30 min.[8] The estimated cost of PONV to a busy ambulatory surgical unit was estimated to range from $0.25 million to $1.5 million per year in lost surgical revenue.[9] The results of several studies suggest that patients not only rank the absence of PONV as being important,[10] but also rank it more important than an earlier discharge from an ambulatory surgical unit.[11] In one survey, patients were willing to pay up to US$100, at their own expense, for a completely effective antiemetic.[12]

The first PONV consensus guidelines were published in *Anesthesia & Analgesia* in 2003.[13] The current guidelines are developed under the auspices of The Society of Ambulatory Anesthesia (SAMBA).[14] The panel reviewed new literature since the previous consensus guidelines on PONV published in 2003.

GOALS OF GUIDELINES

The panel defined the following goals for the guidelines: 1) identify the primary risk factors for PONV in adults and POV in children; 2) establish factors that reduce the baseline risks for PONV; 3) determine the most effective antiemetic monotherapies and combination therapy regimens for PONV/POV prophylaxis, including pharmacologic and nonpharmacologic approaches; 4) ascertain the optimal approach to treatment of PONV with or without PONV prophylaxis; 5) determine the optimal dosing and timing of antiemetic prophylaxis; 6) evaluate the cost-effectiveness of various PONV management strategies using incremental cost-effectiveness ratio (cost of treatment A - cost of treatment B)/(success of treatment A - success of treatment B); and 7) create an algorithm to identify individuals at increased risk for PONV and to suggest effective treatment strategies.

STRENGTH OF EVIDENCE

A variety of grading systems has been proposed to document the strength of evidence of randomized and observational studies supporting a treatment. The panel decided not to grade the included literature but to base its recommendation exclusively on valid studies with a minimal risk of bias. Thus, recommendations would only be made if they were supported by randomized trials and systematic reviews of randomized trials to document efficacy and harm of antiemetic interventions, and by nonrandomized studies using logistic regression to identify risk factors of PONV.

GUIDELINE 1: IDENTIFY PATIENTS' RISK FOR PONV

Adults

Prophylaxis is indicated only in those patients undergoing surgery who are at increased risk for PONV. To determine which patients are candidates for prophylaxis, several baseline risk factors that are independent predictors of PONV have been identified. The predictors fall into 3 categories: (a) patient-specific, (b) anesthetic, and (c) surgical; these are listed in Table 1. The most prevalent patient-specific risk factors for PONV are female gender, nonsmoking status, and a history of PONV or motion sickness.[3,15–17] Other potential patient-specific risk factors include migraine, young age, anxiety, and an American Society of Anesthesiologists (ASA) low-risk classification.[18,19] Anesthetic risk factors include use of general anesthesia with volatile anesthetics, use of nitrous oxide, and postoperative use of opioids.[3,5–7,18] Patients are at increased risk for PONV during lengthy procedures performed under general anesthesia with volatile agents and with increased consumption of opioids—a response that appears to be dose-related.[2,5,7,17] The association between PONV and type of surgery is well documented; however, controversy exists over whether the association is causal. Some

Risk factors	Points
Female gender	1
Nonsmoker	1
History of PONV	1
Postoperative opioids	1
Sum	0-4

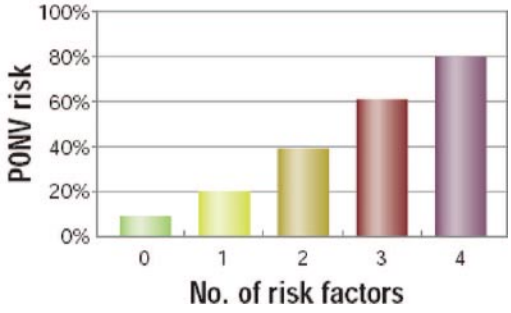

Figure 1. Simplified risk score for PONV in adults; simplified risk score data from apfel et al[3] to predict a patient's risk for PONV. When 0, 1, 2, 3, or 4 of the depicted independent predictors are present, the corresponding risk for PONV is approximately 10%, 20% 40%, 60%, or 80%, PONV, postoperative nausea and vomiting.

Risk factors	Points
Surgery ≥30 min	1
Age ≥3 years	1
Strabismus surgery	1
History of POV or PONV in relatives	1
Sum	0-4

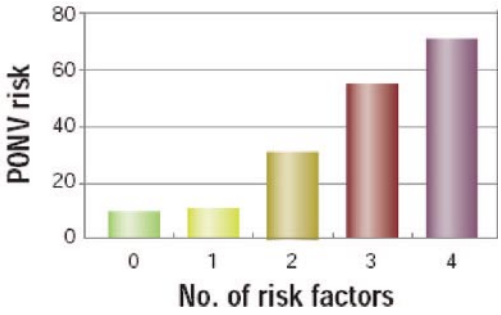

Figure 2. Simplified risk score for PONV in children; simplified risk score data from eberhart et al[20] to predict the risk for POV in children. When 0, 1, 2, 3, or 4 of the depicted independent predictors are present, the corresponding risk for PONV is approximately 9%, 10% 30%, 55%, or 70%, POV, postoperative vomiting; PONV, postoperative nausea and vomiting.

studies suggest that certain types of surgery are independent risk factors for increased PONV,[2,15,17,18,20,21] whereas others indicate that the higher incidence rates are the result of other independent risk factors that correlate with the type of surgery.[3,6,16,19,22] Risk factors that were previously thought to increase the risk for PONV but have now been shown to have no association include obesity, anxiety, and antagonizing neuromuscular block.[16,19,21–24] Because single risk factors for PONV are not sensitive or specific enough to be used to assess risk for PONV, risk models were developed to evaluate PONV risk associated with a number of independent predictors.[3,16] One of the risk models is shown in Figure 1. This simplified model from Apfel et al. shows that the greater the number of independent predictors, the higher the risk for PONV.[3] Specifically, the presence of 1 risk factor correlates with a 20% risk for PONV, and as each subsequent risk factor is added, risk increases by 20%, resulting in an 80% risk when all 4 risk factors are present. It should be noted that risk models estimate PONV risk among patient groups and cannot be used to accurately predict an individual patient's likelihood of having PONV.[19]

Children

A different set of risk factors is used to determine the potential for postoperative vomiting (POV) in children. Eberhart et al. applied a multivariable analysis to determine POV risk factors in children.[25] They identified 4 independent predictors of POV in children: (a) duration of surgery of 30 minutes or longer; (b) age of 3 years or older; (c) strabismus surgery; and (d) a positive history of POV in the patient, a parent, or a sibling. With 1 factor, the POV risk is 10%; the risk increases to 30% with 2, to 55% with 3, and to 70% when all 4 risk factors are present. This simplified risk score is shown in Figure 2. By assessing a patient's risk for PONV, clinicians can decide whether to use prophylactic antiemetics during surgery. To determine whether a patient's risk is sufficiently high to warrant the use of antiemetic prophylaxis, the expected incidence (baseline risk) is multiplied by the relative risk reduction resulting from prophylaxis. Using this calculation, clinicians can determine whether a clinically meaningful decrease in PONV risk will be achieved.[1,26] Exceptions can be made when the risk for vomiting increases medical risk (i.e., patients with wired jaws or increased intracranial pressure, those undergoing gastric or esophageal surgery) or when patients have a strong preference to avoid PONV.

GUIDELINE 2: REDUCE BASELINE RISK FACTORS FOR PONV

One way to decrease the incidence of PONV is to reduce baseline risk factors. The first step is to evaluate whether regional anesthesia can be used instead of general anesthesia. The incidence of PONV is lower in both children and adults with regional anesthesia; in some cases, the incidence is reduced ninefold.[17,27] When general anesthesia is necessary, the recommendation is to use propofol for the induction and maintenance of anesthesia. This can lower the incidence of PONV by 19%, especially within the first 6 hours (number needed to treat [NNT] = 5).[2,28] When propofol is combined with air-oxygen (total IV anesthesia [TIVA]), PONV risk is reduced approximately 25%.[2] Avoiding the use of nitrous oxide and volatile anesthetics can further reduce the incidence of PONV. Volatile anesthetics have been identified as the primary cause of PONV occurring within the first 2 hours.[5] When nitrous oxide or volatile anesthetics are

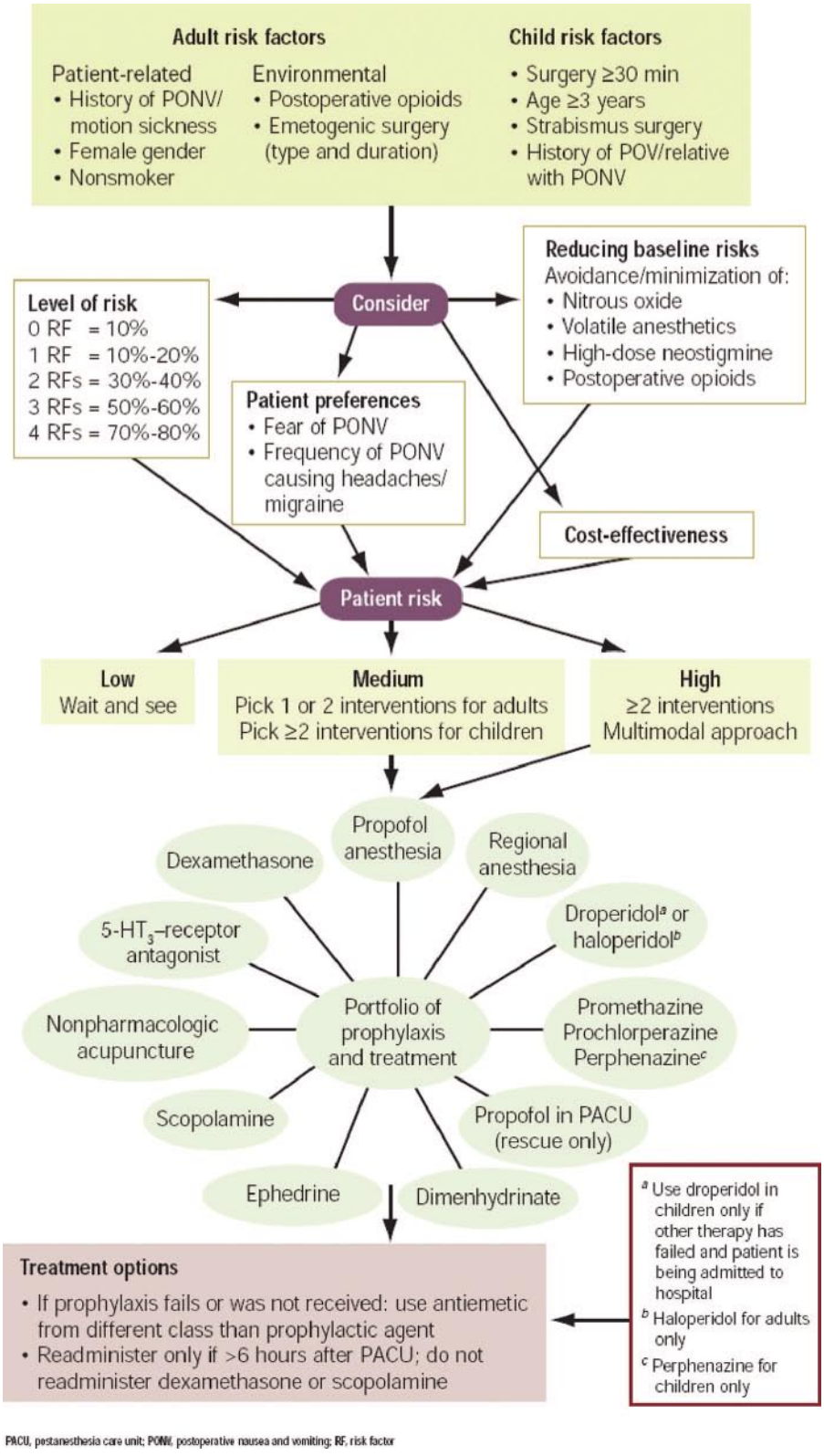

Figure 3. Algorithm for management of PONV.

administered, the incidence of PONV can be as high as 59%.[2] With avoidance of the use of nitrous oxide, PONV risk can be reduced 12%.[2,29,30] Minimizing the use of intra- and postoperative use of opioids further reduces PONV risk.[3,5,7,30] Alternatives to opioids that may have a morphine-sparing effect in the postoperative period include perioperative nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors.[31–33] Minimizing the use of neostigmine or lowering the dose can also reduce baseline PONV risk. High-dose neostigmine (>2.5 mg) is associated with high rates of PONV; dose reduction correlates with reduced PONV risk.[34,35] However, the administration of supplemental oxygen as a means to reduce PONV risk is not recommended because systematic reviews have demonstrated that it has little to

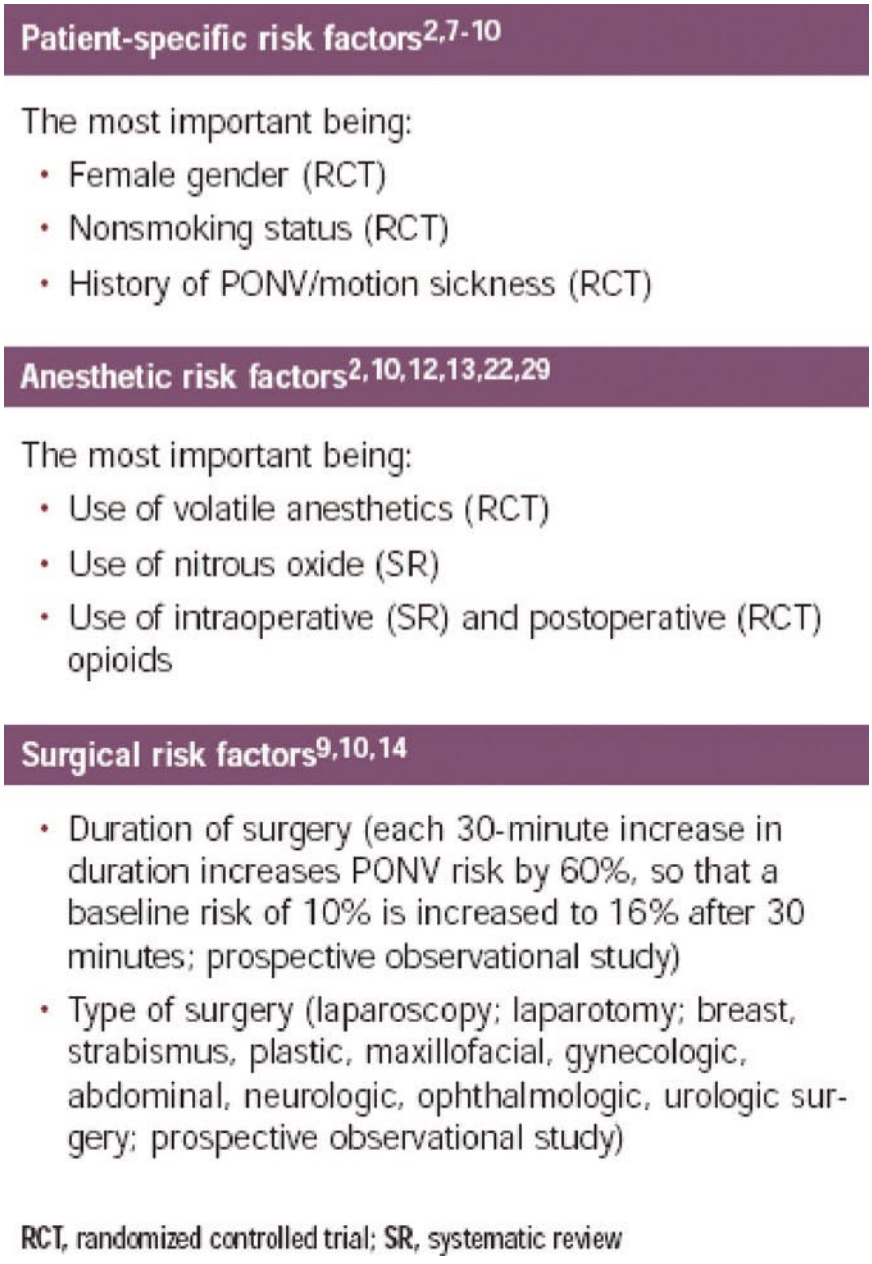

Figure 4. Risk factors for PONV in adults.

no effect.[36,37] Table 2 lists recommended strategies for reducing baseline risk factors.

GUIDELINE 3: ADMINISTER PONV PROPHYLAXIS BY USING 1 TO 2 INTERVENTIONS IN ADULTS AT MODERATE RISK FOR PONV

PONV prophylaxis is not recommended for all patients undergoing surgical procedures, only those considered at moderate to high risk. The PONV management algorithm in Figure 3 outlines the steps to consider when patient risk and subsequent therapy are being determined. For individuals at low risk, a wait-and-see policy is recommended. Adults at moderate risk for PONV should receive combination therapy with 1 or more prophylactic drugs from different classes. The recommended doses and timing of pharmacologic therapies for PONV are given in Table 3. It should be noted that these recommendations are evidence-based and that not all the drugs mentioned have an FDA indication for PONV.

5-HT3–Receptor Antagonists

Four 5-HT3–receptor antagonists have been studied in the prevention of PONV: ondansetron, dolasetron, granisetron, and tropisetron. All of these drugs are most effective when administered at the end of surgery.[38–41] Ondansetron, the most widely studied of the drugs, is recommended at an IV prophylactic dose of 4 mg. Its antivomiting effects are greater than its anti-nausea effects, with an NNT of approximately 6 in. the prevention of vomiting and an NNT of approximately 7 in. the prevention of nausea.[42] Dolasetron also has demonstrated efficacy in preventing PONV when given at an IV dose of 12.5 mg.[39] Granisetron

- Avoidance of GA with use of regional anesthesia[9,22] (RCT)
- Use of propofol for induction and maintenance of anesthesia[3,14] (RCT/SR)
- Avoidance of nitrous oxide[2,3,24,25] (RCT/SR)
- Avoidance of volatile anesthetics[12] (RCT)
- Minimization of intraoperative (SR) and postoperative (RCT/SR) opioids[2,12,13]
- Minimization of neostigmine[29,30] (SR)
- Adequate hydration[69] (RCT)

GA, general anesthesia; **RCT**, randomized controlled trial; **SR**, systematic review

Figure 5. Strategies to reduce baseline risk.

Drug	Dose	Evidence	Timing	Evidence
Dexamethasone	4-5 mg I.V.	SR[41-43]	At induction	RCT[43]
Dimenhydrinate	1 mg/kg I.V.	SR[50] RCT[51,52]	Unknown	N/A
Dolasetron	12.5 mg I.V.	RCT[36]	End of surgery; timing may not affect efficacy	RCT[36]
Droperidol[a]	0.625-1.25 mg I.V.	RCT[44]	End of surgery	SR[45]
Ephedrine	0.5 mg/kg IM	RCT[64]	End of surgery	RCT[64]
Granisetron	0.35-1.5 mg I.V.	RCT[34,35,86]	End of surgery	RCT[34,35]
Haloperidol	0.5-2 mg IM/I.V.	SR[49]	Unknown	N/A
Prochlorperazine	5-10 mg IM/I.V.	RCT[63]	End of surgery	RCT[63]
Promethazine	6.25-25 mg I.V.	RCT[59,96]	At induction	RCT[59,96]
Ondansetron	4 mg I.V.	RCT[81]	End of surgery	SR[33]
Scopolamine	Transdermal patch	SR[53,54]	Prior evening or 4 h before surgery	RCT[54]
Tropisetron	2 mg I.V.	RCT[40]	End of surgery	Expert opinion

Note: These recommendations are evidence-based, and not all the drugs have an FDA indication for PONV.
[a] See FDA black box warning.
N/A, not applicable; **PONV**, postoperative nausea and vomiting; **RCT**, randomized controlled trial; **SR**, systematic review

Figure 6. Antiemetic doses and timing of administration to prevent PONV in adults.

provides effective prophylaxis for PONV at an IV dose range of 0.35 to 1.5 mg, although a systematic review has brought some of these efficacy data into question.[43] Tropisetron is administered prophylactically at an IV dose of 2 mg.[44,45] Overall, the 5-HT3-receptor antagonists are considered equally safe.

Dexamethasone

Dexamethasone, a corticosteroid, is recommended at an IV prophylactic dose of 4 to 5 mg.[46,47] Unlike the recommended timing for the administration of most of the other prophylactic agents, which is at the end of surgery, the recommended timing for the administration of dexamethasone is at the induction of anesthesia.[48] As the large-scale IMPACT trial demonstrated, the efficacy of 4 mg of IV dexamethasone appears to be similar to that of 4 mg of IV ondansetron and 1.25 mg of IV droperidol.[2]

Butyrophenones

Until recently, droperidol was one of the preferred agents for PONV prophylaxis when given IV at a dose between 0.625 and 1.25 mg at the end of surgery.[49,50] However, a black box warning by the FDA led to a reduction in the use of this drug because of potential cardiovascular risks. It should be noted that the doses of droperidol used for the management of PONV are very low and not likely to be associated with significant cardiovascular events.[51,52] In making these recommendations, the panel registered concern about the validity of the FDA conclusion and concluded that droperidol would have been their first choice for PONV prophylaxis if not for the black box warning. Studies have shown equal efficacy rates for droperidol and ondansetron, with an NNT of approximately 5 for the prevention of nausea and vomiting within 24

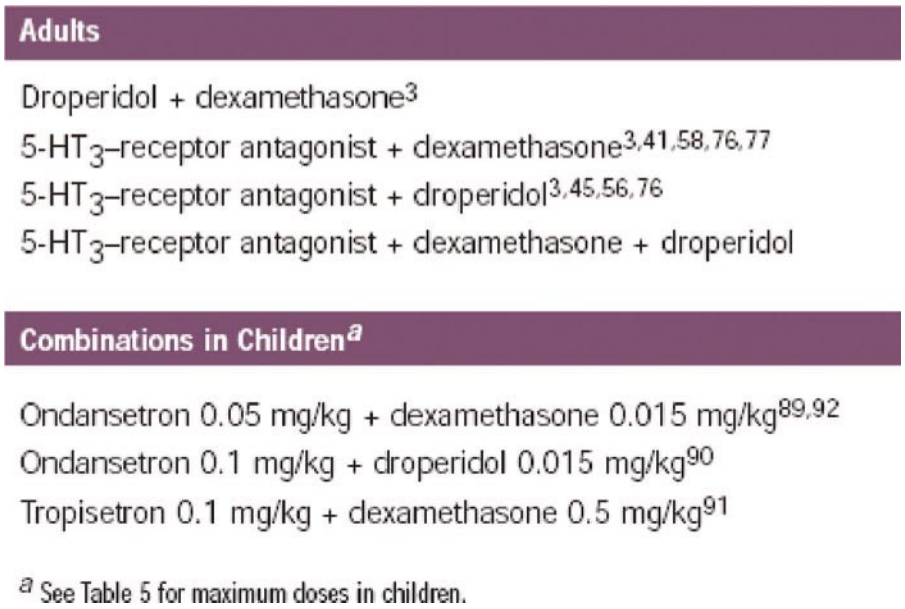

Figure 7. Pharmacologic combination therapy for adults and children.

hours.[1,3] When given with patient-controlled analgesia (PCA), the NNT of droperidol is approximately 3.48. As an alternative to droperidol, haloperidol appears to be effective at IM or IV doses much lower than those used to treat psychiatric disorders, 0.5 to 2 mg, with an NNT of between 4 and 6.49. At higher doses, haloperidol has been associated with sedation, cardiac arrhythmias, and extrapyramidal symptoms; however, in the doses used to prevent PONV, sedation did not occur, no cardiac arrhythmias were reported, and only 1 of 806 patients had extrapyramidal symptoms with a dose of 4 mg.[49] However, because haloperidol carries a risk for QTc interval prolongation, it is not recommended as first-line therapy.

Dimenhydrinate

The antihistamine dimenhydrinate, in a recommended IV dose of 1 mg/kg, has antiemetic efficacy similar to that of the 5-HT3–receptor antagonists dexamethasone and droperidol.[53–55] Data on optimal timing of administration, dose response, and side effects are lacking for dimenhydrinate.

Transdermal Scopolamine

Transdermal scopolamine, administered as a patch the evening before a scheduled surgical procedure or 4 hours before the end of anesthesia, has an NNT of 6.[56,57] Although useful as adjunctive PONV therapy, its drawback is a slow onset of effect, which can be 2 to 4 hours.

Combination Therapy

Meta-analyses have demonstrated the superior efficacy of combination therapy compared with monotherapy for PONV prophylaxis.[58,59] Whenever possible, it is preferable to optimize efficacy by combining drugs with different mechanisms of action (Table 4). For example, drugs with superior antiemetic activity, like the 5-HT3-receptor antagonists, should be used in combination with a drug like droperidol, which has greater anti-nausea efficacy and is protective against headache, a known side effect of the 5-HT3–receptor antagonists.[1] Unfortunately, there is a paucity of data on combination therapy for PONV. The 5-HT3-receptor antagonists have successfully been used in combination with dexamethasone in 1 trial and with promethazine in another; however, optimal antiemetic dosing needs to be established when the drugs are used in combination.[60,61]Evidence suggests that when combined with another drug, dexamethasone should not be given in IV doses exceeding 10 mg, droperidol should not be given in IV doses exceeding 1 mg, and ondansetron should not be given in doses exceeding 4 mg; doses of ondansetron can often be much lower.[1]

Lack of Evidence of Effect

Drugs that have been proven ineffective for PONV prophylaxis include metoclopramide (10 mg IV), ginger root, and cannabinoids (e.g., nabilone, tetrahydrocannabinol).[62–64] In addition, because of a paucity of data on promethazine at an IV dose of 12.5 to 25 mg, prochlorperazine at an IV dose of 5 to 10 mg, and ephedrine at an IV dose of 0.5 mg/kg, these drugs cannot be recommended first-line therapy.[61,65,66] Similarly, not enough data are available to support recommending hypnosis as a modality for PONV prophylaxis.

Nonpharmacologic Prophylaxis

In several clinical trials, acupuncture, acupressure, acupoint stimulation, and transcutaneous electrical nerve stimulation (TENS) had antiemetic efficacy rates comparable with that of pharmacologic therapy (NNT $\approx$ 5, <6 hours after surgery).[67–70] Stimulation of the P6 acupuncture point was as effective as the administration of ondansetron in comparisons with

Drug	Dose	Evidence
Dexamethasone	150 mcg/kg up to 5 mg	SR[41,87]
Dimenhydrinate	0.5 mg/kg up to 25 mg	SR[50]
Dolasetron	350 μmcg/kg up to 12.5 mg	RCT[83,84]
Droperidol[a]	10-15 μmcg/kg up to 1.25 mg	SR[45]
Granisetron	40 mcg/kg up to 0.6 mg	RCT[86]
Ondansetron[b]	50-100 mcg/kg up to 4 mg	SR[37,82]
Perphenazine[c]	70 mcg/kg up to 5 mg	RCT[88]
Tropisetron	0.1 mg/kg up to 2 mg	SR[39]

Note: These recommendations are evidence-based, and not all the drugs have an FDA indication for PONV.

[a] See FDA black box warning. Recommended dose is 10 to 15 mcg/kg.

[b] Approved for POV in pediatric patients aged 1 month or older.

[c] I.V. formulation of perphenazine is no longer available in the United States, only the oral formulation.

POV, postoperative vomiting; RCT, randomized controlled trial; SR, systematic review

Figure 8. Antiemetic doses for prophylaxis of PDV in children.

controls ($P = 0.006$), especially for reducing the incidence of nausea, which was 19% with P6 stimulation, 40% with ondansetron, and 79% with placebo.[68]

Novel Therapies

Several novel drugs show promise in the prevention and treatment of PONV. These include the opioid antagonists naloxone, nalmefene, and alvimopan and the neurokinin-1 (NK1) receptor antagonists CP-122721, GR205171, and aprepitant. Naloxone, when given at low doses (0.25 μg/kg per hour), decreased the incidence of PONV, reduced the need for rescue medication in adults, and reduced opioid-related side effects in children.[71,72] Nalmefene had similar effects, reducing opioid-induced nausea and vomiting and the need for rescue medication in patients receiving PCA.[73] In a placebo-controlled trial, 6 mg of alvimopan effectively reduced nausea and vomiting.[74] The NK1-receptor antagonists also proved effective in preventing PONV.CP-122721, significantly reduced vomiting both alone and in combination with ondansetron.[75] Compared with placebo, GR205171 had a significant treatment effect on vomiting ($P < 0.01$).[76] Compared with ondansetron, 40 mg of oral aprepitant showed equal efficacy in the prevention of nausea and in reducing the need for rescue medication (24 hours postoperatively) and was significantly superior in the prevention of vomiting ($P < 0.001$).[77]

GUIDELINE 4: ADMINISTER PROPHYLACTIC THERAPY WITH COMBINATION (>2) INTERVENTIONS/MULTIMODAL THERAPY IN PATIENTS AT HIGH RISK FOR PONV

Among patients at high risk for PONV, prophylaxis with combination therapy that includes 2 or more interventions is recommended (Fig. 3). In this group of patients, baseline risk factors should be reduced, regional anesthesia should be used whenever possible, and when general anesthesia is needed, factors that could increase PONV risk should be minimized or avoided. Adjunctive therapy including nonpharmacologic approaches should also be considered. The recommended antiemetics for prophylaxis in adults are shown in Table 3, and those recommended for prophylaxis in children are shown in Table 5. Combination therapies with evidence-based efficacy are shown in Table 4. F8

When combination therapy for PONV prophylaxis is being selected, drugs from different classes should be chosen to optimize their effects. Systematic reviews evaluating the efficacy of various combinations have shown that using 5-HT3–receptor antagonists in combination with either dexamethasone or droperidol is a more effective strategy than using monotherapy with any of these drugs.[2,46,58,78,79] The combination of droperidol and dexamethasone is more effective than either agent alone.[2] A comparison of the various combinations found no significant differences between a 5-HT3-receptor antagonist plus droperidol, a 5-HT3–receptor antagonist plus dexamethasone, and droperidol plus dexamethasone.[2,79] However, metoclopramide, used in combination with any of these drugs, did not reduce PONV to a greater extent than monotherapy, further evidence of the lack of support for its use.[75,80]

Scuderi et al. demonstrated the efficacy of a multimodal approach to PONV combining pharmacologic and nonpharmacologic prophylaxis as well as strategies to reduce baseline risk.[81] Prophylactic combination therapy was administered with droperidol and dexamethasone at induction and ondansetron at the end of surgery. In addition, preoperative anxiolysis, aggressive hydration, and oxygen were given. TIVA was used with propofol, remifentanil, and ketorolac. The use of nitrous oxide and neuromuscular blockade was avoided. With this approach, Scuderi et al. found

a 98% complete response rate among patients who received multimodal therapy, a 76% response rate among patients who received prophylactic antiemetic monotherapy, and a 59% response rate among those patients given a routine anesthetic plus placebo.

GUIDELINE 5: ADMINISTER PROPHYLACTIC ANTIEMETIC THERAPY TO CHILDREN AT INCREASED RISK FOR POV—AS IN ADULTS, COMBINATION THERAPY IS MOST EFFECTIVE

Children are at greater risk for POV than adults, with a rate nearly double that seen in the adult population.[82] As a consequence, POV prophylaxis should be more aggressive, consisting of combination therapy with 2 or 3 prophylactic drugs from different classes for patients at either moderate or high risk. The recommended prophylactic antiemetics for children are shown in Table 5.

The 5-HT3–receptor antagonists are the first-line therapy for the prophylaxis of POV in children because findings from meta-analyses and single studies have demonstrated their superiority to droperidol and metoclopramide. In general, the 5-HT3–receptor antagonists as a group have greater efficacy in the prevention of vomiting than of nausea, which is pivotal to preventing POV in children. Ondansetron is one of the most widely studied drugs for POV prophylaxis in children.[83,84] The only prophylactic antiemetic with a pediatric indication, ondansetron is approved for use in children aged 1 month or older.[83] The recommended dose range is 50 to 100 μg/kg.[84] Placebo-controlled trials have shown that ondansetron has an NNT between 2 and 3 to prevent early (0–6 hours) and late (0–24 hours) vomiting.[84] Dolasetron is also effective for POV prophylaxis, with an optimal dose of 350 μg/kg.[85–87] Although very few trials have been conducted in the pediatric population with the other two 5-HT3-receptor antagonists, granisetron at a dose of 40 μg/kg and tropisetron at a dose of 0.1 mg/kg appear to significantly reduce the incidence of POV in children.[45,88]

Other effective drugs for pediatric POV prophylaxis include dexamethasone at a dose of 150 μg/kg (NNT $\approx$ 4),[46,89] dimenhydrinate at a dose of 0.5 mg/kg,[55] and perphenazine at a dose of 70 μg/kg (restricted to the oral formulation because the IV formulation is no longer available in the United States).[90] Droperidol may be used in children; however, because of an increased risk for extrapyramidal symptoms and sedation, it is a last resort measure, to be used only in patients being admitted to the hospital. Although the recommended dose range is 50 to 75 μg/kg, the panel considered this too high for children and recommended instead a range of 10 to 15 μg/kg, extrapolated from adult doses (i.e., 0.625–1.25 mg).[50]

Combination therapy is more effective than monotherapy for POV prophylaxis in children.[91–94] Combinations that have demonstrated clinical efficacy are shown in Table 4. When combination therapy is administered to children, dexamethasone doses should not exceed 150 μg/kg, droperidol doses should not exceed 15 μg/kg, and ondansetron doses should not exceed 50 μg/kg.[1]

GUIDELINE 6: PROVIDE ANTIEMETIC TREATMENT TO PATIENTS WITH PONV WHO DID NOT RECEIVE PROPHYLAXIS OR IN WHOM PROPHYLAXIS FAILED

When the treatment of PONV becomes necessary, resulting from either a prior lack or failure of prophylaxis, therapy should be chosen from a pharmacologic class different from that of the initial prophylactic agent; if no prophylaxis was given, a low dose of a 5-HT3–receptor antagonist should be administered.[95,96] The 5- HT3-receptor antagonists are first-line therapy for existing PONV because they are the only drugs that have been adequately studied, and they have all been found to be equally antiemetic.[96,97] The recommended dosing for treatment with the 5-HT3-receptor antagonists is lower than that recommended for prophylaxis: 1.0 mg of ondansetron, 0.1 mg of granisetron, and 0.5 mg of tropisetron (NNT = 4–5).[84,96] Lower doses of dolasetron have not been studied, so 12.5 mg is recommended for treatment. Other therapies for established nausea and vomiting include 2 to 4 mg of IV dexamethasone, 0.625 mg of IV droperidol, and 6.25 to 12.5 mg of IV promethazine.[95,97,98] Propofol, administered in doses of 20 mg as needed, can be considered for rescue therapy in patients still in the PACU and has been found as effective as ondansetron.[99,100] Among patients who have opioid-induced nausea or vomiting, the addition of 2.5 mg of droperidol to every 100 mg of morphine in a PCA device appears to reduce PONV.[101]

If prophylaxis has been given and has failed, the same medication should not be repeated within the first 6 hours after the patient has left the PACU, because this will confer no additional benefit.[102] If more than 6 hours has elapsed, a repeat dose of a 5-HT3-receptor antagonist—droperidol or haloperidol—may be attempted, but only if triple therapy has been used for prophylaxis and no alternatives are available for rescue medication (Fig. 3). The readministration of dexamethasone or transdermal scopolamine is not recommended within 24 hours.

Post-discharge Nausea and Vomiting

Post-discharge nausea and vomiting (PDNV) is a substantial problem following ambulatory surgery, affecting approximately one third of patients.[103] Prophylactic antiemetic therapy may be given before discharge in patients at high risk for PDNV; however, antiemetics with a short half-life may prove ineffective. Prophylactic combination therapy appears to be the best approach, with an NNT of approximately 5 versus an NNT of approximately 12 to 13 for monotherapy with 4 mg of ondansetron or 4 to 10 mg of dexamethasone.[103]

Other effective strategies for reducing the incidence of PDNV include substituting propofol for inhalational anesthesia ($P < 0.05$), using orally disintegrating ondansetron tablets, acupoint stimulation of P6, and transdermal scopolamine.[56,104–106] Droperidol appears to be ineffective at preventing PDNV at a dose of <1 mg, and inadequate information is available to evaluate droperidol at a dose of 1 mg or higher.[103]

SUMMARY

Identification of patients at increased risk for PONV allows targeting antiemetic prophylaxis to those who will benefit most from it. No prophylaxis is warranted for patients at low risk for PONV unless there is risk of medical sequelae from vomiting. The first step in reducing PONV risk is to reduce baseline risk factors. For patients at moderate risk, antiemetics should be used in combination for PONV prophylaxis. The adoption of a multimodal approach to the management of PONV should be considered in patients at high risk for PONV. In patients who develop PONV despite receiving prophylaxis, an antiemetic acting at a different receptor should be used for rescue within the first 6 hours following surgery. After 6 hours, PONV can be treated with any of the drugs used for prophylaxis except dexamethasone and scopolamine.

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Anesthesia for Endovascular Surgery

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Endovascular surgery or interventional radiology refers to treatments for diseases by the delivery of drugs or devices by endovascular access, most commonly arterial. Uses include definitive treatments (aneurysms, stents, thrombolysis), adjuvant treatments (decreasing vascularity, functional testing), and palliative treatments (intra-arterial chemotherapy). There has been a rapid increase in the use and success of these approaches and anesthesiologists are increasingly involved in caring for the patients. In many hospitals these procedures have mainly been done in the Radiology department, but surgeons are now learning these techniques, so that appropriate angiographic equipment is being installed in operating theaters. There is also an ever-expanding list of physicians who have joined the interventionalist ranks, including radiologists, vascular surgeons, neurosurgeons, neurologists, and cardiologists, thereby further increasing the number of possible venues. The medical backgrounds, the training, and the procedure location vary greatly. While cardiologist have led the way in many of these approaches, similar approaches are now being used for all parts of the vascular tree, arterial and venous.

Functions of the anesthesiologist include: 1) maintain physiological stability; 2) maintain patient immobility to improve the quality of images and/or treatment; 3) manage anticoagulation; 4) manipulate systemic or regional blood pressure; 5) treat unexpected complications, e.g., hemorrhage, vascular occlusion; 6) rapid emergence to allow early assessment; and 7) patient transport to and from the Radiology suites.

The safe administration of anesthetic care in a remote location requires careful preparation. If you have not worked at the site before, then visit the venue well in advance of starting the case. Also, speak with the interventionalist so as to have a clear understanding of what will be done, what position will be used, the duration of procedure, and expectations from anesthesia. Unlike surgeons who are usually familiar with communicating significant complications to the anesthesiologist, this may not be the case with other interventionalists. Thus establishing a communication pattern is vitally important.

Before starting, ensure that the following are available:

- O_2 both piped and cylinders
- suction that *reaches* the patient
- anesthetic machine and supplies equivalent to the operating room
- anesthetic cart with all the drugs usually available in the OR
- manual resuscitator bag (e.g., Ambu), resuscitation drugs and immediate availability of a defibrillator
- extensions for the breathing circuit and IV lines; confirm adequacy of IV access before the arms are tucked
- *all* routine monitors
- sufficient electrical outlets
- adequate lighting
- immediate (easy) access to the patient or a mechanism to achieve that
- adequate and suitable padding for patient comfort and to prevent tissue injury
- good and easy two way communication with the radiology staff
- a way to rapidly call for help from anesthesia colleagues as well as equipment, e.g., intubation aids

The choice of anesthetic technique varies among centers, with no clear demonstrated superiority of any of them. However, there is an increasing trend toward general anesthesia, as procedures are getting longer due to complexity. Easily controlled immobility significantly reduces motion artifact in the images and may also allow more precise delivery of the treatment. The choice of general anesthetic technique should be guided by the pathology, comorbidities, and personal preferences. No specific agents have been shown to be superior. Both endotracheal intubation and laryngeal masks are successfully used. In procedures not involving the head and neck, the LMA is often a very suitable choice, but in head/neck procedures one should make sure how the head will be placed and/or moved. It is possible to transduce arterial blood pressure and obtain blood samples from the femoral arterial sheath, but this is frequently damped by the intra-arterial catheters, and it may be preferable to have a separate (radial) arterial catheter.

Intravenous sedation can be used to relieve anxiety, pain, and discomfort while keeping the patient cooperative enough to breath-hold or be immobile when requested. For intra-abdominal vascular procedures, regional techniques (epidural/spinal) supplemented

by sedation can also be used. The intra-arterial insertion of multiple catheters may cause limb ischemic pain, which is well managed with a regional. CSF drainage may also form part of spinal cord protection during proximal aortic procedures. Proposed management of a bloody tap in a patient who will be anticoagulated needs to be discussed with all participants in advance. Care should be used with nasopharyngeal airways, as they may cause troublesome bleeding in anticoagulated patients.

Anticoagulation is required to prevent thromboembolic complications and the protocol to be used should be discussed in advance. After a baseline ACT, IV heparin as repeated boluses or an infusion is usually given so as to maintain the ACT at 2–3 times normal. Protamine should always be immediately available and, after communication with the interventionalist, should be given if there is hemorrhage and also at the end of the procedure as guided by ACT. In patients with heparin-associated thrombocytopenia, direct thrombin inhibitors may be used. Sometimes antiplatelet drugs (e.g., abciximab, ticlopidine) are also given in the management of thromboembolic complications, but their effects are hard to monitor or reverse.

Deliberate hypertension may be beneficial when there is acute arterial occlusion, including from emboli, and in patients with (cerebral) vasospasm. The aim is to try and improve collateral blood flow. Hypotension is used much less frequently but is sometimes useful to test cerebrovascular reserve during trial occlusion and to slow flow during the injection of arteriovenous malformations.

Angioplasty and stents are also increasingly being used to treat carotid stenosis in lieu of carotid endarterectomy. Distension of the carotid artery may cause significant bradycardia, which usually responds to atropine or glycopyrrolate, but has been reported to require external pacing. Equipment for the latter must be immediately available. Other complications include thromboembolism, dissection, transient ischemic episodes, and stroke.

In conclusion, endovascular approaches to the treatment of disease is a rapidly growing field and will no doubt become a large component of our practices. The delivery of this care will take place in the OR as well as potentially multiple sites around the hospital, including radiology, cardiology, and other departments. We need to strive to consolidate these activities or achieve a uniform level of care at all the (remote) sites.

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Labor and Delivery Management of the Morbidly Obese Parturient

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CASE PRESENTATION

S.E. is a 28-year old G2P1 undergoing induction at term for worsening chronic hypertension. Her current weight is 520 lbs. (236 kg, BMI 84). She has a history of asthma for which she uses a steroid inhaler QID and an inhaled bronchodilator PRN. Obstructive sleep apnea was diagnosed by sleep study, and she has been on a 3L nasal cannula during her final trimester of pregnancy with an oxygen saturation of 94%. She is confined to a wheelchair because of dyspnea on exertion. Her first pregnancy was delivered by cesarean section using epidural anesthesia; at that time she weighed 300 lbs. Her obstetrician plans a trial of labor.

Care of the morbidly obese parturient is a challenge for the obstetricians, anesthesiologists, and nurses involved in her delivery. Studies of obesity during pregnancy use body mass index (BMI) to define obesity, where BMI = weight in kg/height in m^2 and BMI >40 is morbidly obese. Using those criteria, 6–10% of parturients are morbidly obese. Morbid obesity is associated with numerous adverse pregnancy outcomes (OR = odds ratio).[1,2,3]

- Preeclampsia OR 4.82
- Gestational diabetes OR 4.00
- Fetal macrosomia OR 3.82
- Neonatal death OR 3.41
- Gestational hypertension OR 3.20
- Shoulder dystocia OR 3.14
- Meconium aspiration OR 2.85
- Intrauterine fetal demise OR 2.79
- Cesarean delivery OR 2.69
- Fetal distress OR 2.52
- Instrumental delivery OR 1.34

It has been estimated that 1 in. 7 cesarean deliveries may be due to obesity.[4] Both fetal neural tube defects[5] and the risk of fetal/neonatal death are increased in obese women compared to normal weight parturients.[6] At weeks 28–36, the odds ratio of fetal death compared to normal weight women was 2.1, at weeks 37–39 it was 3.5, and at 40+ weeks the odds ratio was 4.6.[6] The risk for stillbirth increases in a dose-dependent fashion with increases in BMI; OR 1.9 for BMI >40.[7]

The cardiac and pulmonary physiologic changes associated with obesity are well known.[8] Although all pregnant women are considered to be "full stomach" patients, obesity may or may not increase that risk. Gastric emptying of clear liquids does not seem to be delayed in obese pregnant patients. A small study showed *no* difference in gastric emptying times for 50 or 300 mL water, and the emptying times were similar to non-obese pregnant and non-pregnant women (~30 minutes).[9] In contrast, two studies in non-pregnant subjects found strong correlations between increasing BMI and reflux symptoms, with OR 6.3 for women with BMI >35.[10,11]

Increasing BMI is associated with increased rates of cesarean delivery.[12] Nulliparous women with a BMI >35 in. the first trimester had an increased rate of cesarean delivery following onset of spontaneous labor at term when compared to women with BMI <25 (OR 3.8). For parturients attempting vaginal birth after cesarean delivery (VBAC), success rates are lower and infection rates higher as BMI increases. Both BMI >29 and pregnancy weight gain >40 pounds decreased the chance of successful VBAC.[13] Overall success rate of VBAC was 77%, but with BMI >29 the success rate was 68%, and with >40 pound weight gain the success rate was only 67%. A prospective observational study compared 14,142 women having trial of labor after one prior cesarean to 14,304 women having an elective repeat cesarean.[14] The authors found that increasing BMI was directly associated with failed trial of labor, from 15.2% in normal weight to 39.3% in morbidly obese women. Among morbidly obese women, trial of labor carried greater than five-fold risk of uterine rupture/dehiscence (2.1% vs 0.4%) and risk of neonatal injury (1.1% vs 0.2%). Morbidly obese women failing a trial of labor and then requiring cesarean had a six-fold greater composite maternal morbidity than those undergoing a successful trial of labor (14.2% vs 2.6%). Consequently, it may be more cost effective to simply offer an elective cesarean delivery to patients weighing more than 300 pounds.[15,16] A study of 298 deliveries to parturients with a history of bariatric surgery (both laparoscopic and open) also found an increased risk of cesarean delivery (OR 2.4) but no other adverse perinatal outcomes.[17]

Recent publications have highlighted the contribution obesity makes to anesthesia-related maternal mortality. A review of maternal deaths in Michigan found that 75% of the 8 anesthesia-related maternal

deaths involved obese parturients.[18] All occurred during emergence (*not* induction) from general anesthesia or sedation and involved hypoventilation or airway obstruction. These cases raise questions of appropriate PACU management after general anesthesia on L&D and the use of additional monitoring for obese patients at risk for sleep-obstructed breathing. Great Britain published their "Confidential Enquiry into Maternal and Child Health, Saving Mother's Lives, 2003–2005", the seventh report from the United Kingdom.[19] Four of their six direct anesthetic deaths involved obese women; three with postoperative respiratory failure after spinal or general anesthetics. They emphasize the additional care and expertise required for safe anesthetic care of obese parturients.

When you are faced with a morbidly obese parturient, it is important to have a flexible anesthetic plan. Despite a planned induction of labor or spontaneous onset of labor, the patient may still require an urgent cesarean delivery due to failure to progress or an emergent cesarean for maternal or fetal complications. Be prepared for anything!

PREOPERATIVE MANAGEMENT

The LDR and operating room should be prepared with a bed of appropriate width and strength, wider arm supports and pads, and a ventilator capable of high peak airway pressures. Many operating room beds are only rated for weights to 300 pounds. Additional items may be needed for regional and general anesthesia such as longer spinal and epidural needles and difficult airway equipment. The patient should be interviewed early in the course of labor, or preferably during an antepartum visit. Be frank about the additional problems posed by her obesity and make recommendations about how these will be managed. If the patient is seen antepartum, consider additional tests such as a chest film with shielding to assess heart size, 12-lead electrocardiogram, sleep study, and/or pulmonary function tests with arterial blood gases – but only if those tests will affect your management.

When the patient arrives on L&D, help nursing personnel obtain adequate IV access. An arterial line should be considered if the arms are excessively obese or their shape makes it difficult to correctly wrap a cuff. Assess the airway carefully. BMI alone does *not* predict difficulty with intubation. Several studies have shown that the best predictors of difficult laryngoscopy in obese patients are Mallampati class ≥ 3 and large neck circumference.[20,21,22] Aspiration prophylaxis should be administered early and continued throughout labor. An H_2 receptor antagonist, metoclopramide, and a clear antacid should all be considered. If intubation will be required, administer an anticholinergic agent to decrease secretions. Supplemental oxygen should be administered throughout labor and delivery with continual monitoring of oxygen saturation. Alert your colleagues that you have a complicated patient so that additional experienced hands can be available in case of an emergency delivery. Discuss plans with your obstetricians for *any* eventuality - a trial of labor and vaginal delivery, labor followed by cesarean delivery for failure to progress (non-urgent), or emergency cesarean delivery for fetal distress. They should understand that nothing can be done STAT with this patient.

REGIONAL ANESTHESIA

A spinal or epidural catheter should be inserted early in labor in case fetal distress occurs. Landmarks will be difficult to palpate so optimize what you can. Have the patient in a sitting position. Use ultrasound guidance to identify midline bony structures, the distance from the skin to the epidural space, and the intervertebral space.[23] Using ultrasound imaging in non-obese parturients, the success of the initial insertion point chosen was 92%, with no need to redirect in 74%. Correlation with depth was 0.881. Even small directional errors are exaggerated with increasing depth of the epidural space. Infiltrate generously and be patient. The patient can often help guide you to the midline by telling you if she senses pressure or pain from your needle advancement to her left or right. It is rare to need an extra-long epidural needle in the midline approach, but it is appropriate to have one available. Thread the catheter *at least* 5 cm into the space and secure well. Position the patient sitting upright or lateral recumbent before securing the catheter to allow inward movement without dislodgement.[24] Minimizing motor block during labor will aid nursing care.

Consider a *planned* "wet tap" with your epidural needle, or if one occurs unexpectedly, consider converting to a continuous spinal anesthetic, administering dilute local anesthetic and opioid for labor (e.g., 0.125% bupivacaine with fentanyl 5 μg/mL at 1–2 mL/h or ~3 mL/h of the usual epidural infusion solution) or more concentrated local anesthetics for operative or cesarean delivery (e.g., 1–3 mL 0.5% bupivacaine in increments, with 25 μg fentanyl and 0.25 mg morphine). Post-dural puncture headaches occur rarely in morbidly obese patients.[25] Although spinal catheters may dislodge as frequently as epidural catheters, they are easier to assess by simply attempting to withdraw spinal fluid, and replacement can be started more expeditiously. When epidural catheters dislodge it is often only discovered when an attempted top-up dose fails to provide relief. Expect to replace the catheter eventually, as 44% require replacement at least once, and 20% >2 times.[26] Dose cautiously! Local anesthetic requirements for spinal and epidural anesthesia may be reduced and are certainly unpredictable. Adequate respiration is maintained even with a block to T5, but continuous oxygen administration by nasal cannula and monitoring with pulse oximetry are necessary. For cesarean delivery, place the block in the operating room to avoid the

necessity of moving the patient once motor block has occurred. Both the abdominal fat pad and the gravid uterus will contribute to supine hypotension. Position and pad carefully for what may be a lengthy surgery. Accept *only* a perfect block before allowing the surgeons to make skin incision.

GENERAL ANESTHESIA

Additional experienced hands must be available, plus ancillary airway equipment such as a fiberoptic bronchoscope, short-handled laryngoscope, assortment of laryngeal mask airways, etc. Obesity alone does *not* predict a difficult airway.[9,10] If a rapid sequence induction seems inadvisable, consider awake oral intubation with topical anesthesia. Aspiration prophylaxis and a drying agent should have been administered previously. In the obstetric patient, minimal sedation should be given to avoid newborn respiratory depression. The mucosa is friable during pregnancy and nasal intubations are problematic due to bleeding. Landmarks for blocks (e.g., superior laryngeal, transtracheal) will be obscure in the obese patient. Nebulized 4% lidocaine is an option for topical anesthesia. Full-stomach precautions should be balanced with the need for adequate airway anesthesia. Use continuous oxygen supplementation.

The patient should be fully denitrogenated prior to a rapid sequence induction. Positioning is extremely important: the head, neck and shoulders should be raised so that there is a straight line between the sternal notch and the external auditory meatus.[27] The patient should be in reverse Trendelenburg position until the airway is secure.[28] Pre-oxygenation in the head-up position was more effective at achieving higher oxygen tensions and increasing the desaturation period in non-obstetric patients, and the same should be true for cesarean delivery.[29] A laryngeal mask airway or equivalent should be immediately available in case ventilation is necessary and mask ventilation is difficult.[30] Drug doses may be based on actual or ideal body weight.[31] Highly lipophilic medications (barbiturates, benzodiazepines) have a significantly increased volume of distribution compared to non-obese patients, so their dosages are increased but their elimination half-lives are longer. Non- or weakly lipophilic drugs are administered based on lean body mass.[32] Administer sufficient succinylcholine to provide optimal intubating conditions. Atracurium is preferable to vecuronium, rocuronium and cisatracurium in terms of predictability of duration.[33,34,35]

Be prepared for prolonged surgery, and optimize padding and positioning once asleep. Remember the hemodynamic and ventilatory consequences of the abdominal fat pad in the supine position.[36] Expect increased blood loss and assure adequate IV access. Extubate conservatively and in the reverse Trendelenburg position. The incidence of dangerous post-extubation obstruction is ~5% in patients with obstructive sleep apnea, so extubate with oral or nasal airways in place. If there are concerns about re-intubation, extubate over an airway exchange catheter.

POSTOPERATIVE CONSIDERATIONS

The patient should be kept in the semi-recumbent or reverse Trendelenburg position during the recovery period. Thromboembolism and pulmonary complications are the patient's greatest postoperative risk, consequently good analgesia is important to encourage mobilization. Analgesia with neuraxial opioids with or without local anesthetics is preferable to IM (IM) injections. Since IM injections will likely be deposited in fat, IV patient-controlled analgesia (PCA) is preferable if no spinal or epidural catheter is present. Dose on the basis of ideal body weight and avoid a basal rate. The combined use of non-steroidal anti-inflammatory medications should be considered to improve analgesia without additional respiratory depression.

Continue respiratory monitoring for hypoxia and hypoventilation and consider CPAP if the patient has obstructive sleep apnea. A monitored or step-down bed may be a more appropriate location for recovery than L&D if respiratory issues are a concern. Mobilization and incentive spirometry are key in preventing postoperative complications. Begin anti-coagulation soon after surgery with low molecular weight or unfractionated heparin. Later complications are wound infection and dehiscence as well as thromboembolism. These may require another trip to the operating room, and many of the same principles will apply.

CONCLUSIONS

The risks of anesthesia, surgery, and childbirth are higher in obese patients, and the prevalence of obesity in parturients is increasing. Two recent ACOG publications address care of the obese parturient. *The Role of the Obstetrician-Gynecologist in the Assessment and Management of Obesity* notes that all patients should have a BMI calculated and should be offered interventions and counseling when appropriate.[37] *Obesity in Pregnancy* addresses pre-conception counseling and peripartum care.[38] Certainly the risk of dying prematurely increases for people who are overweight. In developing countries, obesity is associated with affluence, while in industrialized countries it is usually associated with poverty. Unlike most parturients, medical disease commonly complicates care of the morbidly obese patient. Their anesthetic management requires patience, planning, and collaboration.

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Neurologic Complications of Peripheral Nerve Blocks

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Perioperative nerve injuries have long been recognized as a complication of regional anesthesia. Fortunately, severe or disabling neurologic complications rarely occur. Risk factors contributing to neurologic deficit after regional anesthesia include neural ischemia (hypothesized to be related to the use of vasoconstrictors or prolonged hypotension), traumatic injury to the nerves during needle or catheter placement, infection, and choice of local anesthetic solution.[1–3] In addition, postoperative neurologic injury due to pressure from improper patient positioning or from tightly applied casts or surgical dressings, as well as surgical trauma are often attributed to the regional anesthetic.[4] Lynch et al.[5] reported a 4.3% incidence of neurologic complications following total shoulder arthroplasty. The neurologic deficit localized to the brachial plexus in 75% of affected patients. Importantly, the level of injury occurred most commonly at the upper and middle nerve trunks- the level at which an interscalene block is performed, making it impossible to determine the etiology of the nerve injury (surgical versus anesthetic). Patient factors such as body habitus and preexisting neurologic dysfunction may also contribute. For example, the incidence of peroneal nerve palsy following total knee replacement is increased in patients with significant valgus or a preoperative neuropathy (Table 1).[6,7]

The safe conduct of regional anesthesia involves knowledge of the large patient surveys as well as individual case reports of neurologic deficits following regional anesthetic techniques. Prevention of complications, along with early diagnosis and treatment are important in the management of regional anesthetic risks.

INCIDENCE AND ETIOLOGY OF NEUROLOGIC COMPLICATIONS

A prospective survey in France recently evaluated the incidence and characteristics of serious complications related to regional anesthesia.[1] A total of 103,730 regional anesthetics, including 21,278 peripheral nerve blocks, were performed over a five-month period. The incidence of cardiac arrest and neurologic complications was significantly higher after spinal anesthesia than other types of regional procedures (Table 2). Neurologic complications related to the regional anesthetic technique occurred in 34 patients; recovery was complete within three months in 19 of 34 patients. In all cases of nerve injury peripheral block, needle placement was associated with either paresthesia during needle insertion, or pain with injection. In all cases, the postoperative deficit had the same topography as the associated paresthesia. The authors concluded that needle trauma and local anesthetic neurotoxicity were the etiologies of most neurologic complications. This study demonstrated that the incidence of severe anesthesia-related complications is very low. However, since serious complications were noted to occur even in the presence of experienced anesthesiologists, continued vigilance in patients undergoing regional anesthesia is warranted. In a follow-up study involving over 150,000 regional anesthetics, Auroy et al.[8] reported a decrease in the frequency of serious complications related to the anesthetic technique.

Cheney et al.[9] examined the American Society of Anesthesiologists Closed Claims database to determine the role of nerve damage in malpractice claims filed against anesthesia care providers. Of the 4,183 claims reviewed, 670 (16%) were for anesthesia-related nerve injury. The most frequent sites of injury were the ulnar nerve (190 claims), brachial plexus (137 claims), lumbosacral roots (105 claims), or spinal cord (84 claims). Regional anesthesia was more frequently associated with nerve damage claims. Ulnar nerve injuries were more often associated with general anesthesia. However, spinal cord and lumbosacral nerve root injuries having identifiable etiology were associated predominantly with a regional anesthetic technique, and were related to paresthesias during needle or catheter placement or pain during injection of local anesthetic. It is also notable that despite intensive medicolegal investigation, a definite mechanism of injury is rarely determined. The lack of apparent mechanism often led the patient (and consulting specialists) to assume that something most have been done incorrectly during the perioperative period to cause the nerve injury.

NERVE INJURY FROM NEEDLE AND CATHETER PLACEMENT

Many anesthesiologists intentionally elicit a paresthesia during the performance of peripheral regional techniques. Although the elicitation of a paresthesia may represent direct needle trauma and increase the risk of persistent paresthesia associated with regional anesthesia, there are no clinical studies that definitively either prove or refute the theory.[10–13] Selander

Table 1. Risk Profile for Peroneal Nerve Palsy After Total Knee Arthroplasty

Risk factor	Peroneal palsy (n = 8)	No peroneal nerve palsy (n = 353)
Age (yr)	64 ± 10	69 ± 10
Valgus (degrees)	13 ± 5*	9 ± 7
Tourniquet time (min)	141 ± 52*	103 ± 28
Neurologic condition	4*	30
Anesthetic technique	3	112
General		
Spinal	1	67
Epidural	4	174
Epidural analgesia	4**	104
Postoperative bleeding	3*	4

* $P < 0.05$.

** Although postoperative epidural analgesia was not a risk factor for peroneal nerve palsy, all cases of peroneal nerve palsy with motor deficits occurred in patients with postoperative epidural analgesia. Adapted from Horlocker et al. (6). Used with permission.

et al.[10] reported a higher incidence of postoperative nerve injury in patients where a paresthesia was sought during axillary block (2.8%) compared to those undergoing a perivascular technique (0.8%). However, the difference was not significant. Importantly, 40% of patients in the perivascular group reported unintentional paresthesias during the procedure, demonstrating the difficulty with standardization of technique and analysis of neural injury. Postoperative neurologic deficits ranged from slight hypersensitivity to severe paresis, and persisted from two weeks to greater than one year. In a prospective study utilizing a variety of regional anesthetic approaches including paresthesia, transarterial and nerve stimulator techniques, Urban and Urquhart[12] noted that mild paresthesias were common the day after surgery, occurring after 9% of interscalene blocks and after 19% of axillary blocks. At two weeks the incidence had decreased significantly, with near complete resolution noted at four weeks. Stan et al.[11] reported a 0.2% incidence of neurologic complications after axillary blocks performed with the transarterial approach. However, vascular complications such as transient arterial spasm, unintentional vascular injection and hematoma formation occurred in 1.4% of patients. Theoretically, localization of neural structures with a nerve stimulator would allow a high success rate without increasing the risk of neurologic complications, but this has not been formally evaluated. Fanelli et al.[13] prospectively evaluated 3996 patients undergoing sciatic-femoral, axillary, and interscalene blocks using a multiple injection/nerve stimulator technique. During the first month after surgery, 69 patients (1.7%) developed neurologic dysfunction; recovery was complete in all but one in 4–12 weeks. (This frequency is similar to that reported using a paresthesia technique). The only variable associated with neurologic injury was tourniquet inflation pressure >400 mm | Hg. Use of a nerve stimulator does not prevent intraneural injection. Indeed, serious neurologic injury has been reported following uneventful brachial plexus block using a nerve stimulator technique.[14,15] Equally interesting are the cases in which apparent intraneural injection did not result in neurologic injury.[16,17] Currently, no compelling evidence exists to endorse a single technique as superior with respect to success rate or incidence of complications. Needle gauge, type (short vs long bevel), and bevel configuration may also influence the degree of nerve injury, although the findings are conflicting and there are no confirmatory human studies.[18,19]

The passage and presence of an indwelling catheter into a peripheral nerve sheath presents an additional source of direct trauma. The risk of neurologic complications resulting from plexus or peripheral nerve catheters remains undefined.[20,21] While difficulty during catheter insertion may lead to vessel puncture, tissue trauma and bleeding, significant complications are uncommon and permanent sequelae are rare. In a series of 405 continuous brachial plexus blocks, Bergman et al.[22] reported 9 complications in 8 patients for an overall frequency of 2.2%. Complications included one each of the following: localized infection (treated with catheter removal and antibiotics), axillary hematoma, and retained catheter fragment requiring surgical excision. In addition, two patients reported signs and symptoms of systemic (pre-seizure) local anesthetic toxicity. Four (1.0%) patients reported new neurologic deficits postoperatively. In two patients, the neural dysfunction was non-anesthesia related. In a more recent prospective study involving 1,416 patients with continuous catheters, there were 12 patients (0.84%) experiencing serious adverse events and three (0.21%) patients had neurologic lesions attributed to the continuous peripheral nerve catheter.[23]

Table 2. Complications Related to Regional Anesthesia

Technique	Cardiac arrest	Death	Seizure	Neurologic injury
Spinal (N = 40,640)	26 (3.9–8.9)	6 (0.3–2.7)	0 (0–0.9)	24 (3.5–8.3)
Epidural (N = 30,413)	3* (0.2–2.9)	0 (0–1.2)	4 (0.4–3.4)	6* (0.4–3.6)
Peripheral blocks (N = 21,278)	3+ (0.3–4.1)	1 (0–2.6)	16# (3.9–11.2)	4# (0.5–4.8)
IV regional (N = 11,229)	0 (0–3.3)	0 (0–3.3)	3 (0.5–7.8)	0 (0–3.3)

Data presented are number and (95% confidence interval). * Epidural versus spinal ($P < 0.05$).

+ Peripheral nerve blocks versus spinal ($P < 0.05$). # Peripheral nerve blocks versus epidural ($P < 0.05$).

Adapted from Auroy et al. (1). Used with permission.

LOCAL ANESTHETIC TOXICITY

Neurologic complications following regional anesthesia may be a direct result of local anesthetic toxicity. Although most local anesthetics administered in clinical concentrations and doses do not cause nerve damage, prolonged exposure, high dose and/or high concentrations of local anesthetic solutions may result in permanent neurologic deficits. There is both laboratory and clinical evidence that local anesthetic solutions are potentially neurotoxic and that the neurotoxicity varies among local anesthetic solutions.[2,24–27] Differences in neurotoxicity are dependent on pKa, lipid solubility, protein binding and potency. In histopathologic, electrophysiologic, and neuronal cell models, lidocaine and tetracaine appear to have a greater potential for neurotoxicity than bupivacaine at clinically relevant concentrations.[25,28] Additives such as epinephrine and bicarbonate may also affect neurotoxicity. Addition of 5 μg/mL of epinephrine increases the toxicity of both lidocaine and bupivacaine. The presence of a preexisting neurologic condition may predispose the nerve to the neurotoxic effects of local anesthetics.[6,12] The presumed mechanism is a "double crush" of the nerve at two locations resulting in a nerve injury of clinical significance.[29] The double crush concept suggests that nerve damage caused by traumatic needle placement/local anesthetic toxicity during the performance of a regional anesthetic may worsen neurologic outcome in the presence of an additional patient factor or surgical injury. Finally, intraneuronal injection may potentiate the neurotoxic effects of higher concentrations of local anesthetic as well as the addition of vasoconstrictors.

NEURAL ISCHEMIA

Peripheral nerves have a dual blood supply consisting of intrinsic endoneural vessels and extrinsic epineural vessels. A reduction or disruption of nerve blood flow may result in neural ischemia. Intraneural injection of volumes as small as 50-l00 μL may generate intraneural pressures which exceed capillary perfusion pressure for as long as 10 minutes and thus cause neural ischemia.[30] Endoneural hematomas have also been reported after intraneural injection.[19] Epineural blood flow is also responsive to adrenergic stimuli.[31,32] The use of local anesthetic solutions containing epinephrine theoretically may produce peripheral nerve ischemia, especially in patients with microvascular disease.[2,26]

Neural ischemia may also result from expanding hematoma. In the series of 1000 transarterial axillary blocks, Stan et al.[11] reported vascular complications such as transient arterial spasm, unintentional vascular injection and hematoma formation occurred in 1.4% of patients. A case report of axillary block complicated by hematoma and radial nerve injury has been described.[33]

Few data exist on the risk of hemorrhagic complications in patients undergoing peripheral block while receiving hemostasis-altering medications. Although the Consensus Statements on Neuraxial Anesthesia and Anticoagulation published by the American Society of Regional Anesthesia[34] could be applied to any regional anesthetic technique, a more liberal application, taking into account the compressibility of the needle insertion site and the vascular structure at risk.[35–37] Bleeding into a nerve sheath does not represent the same catastrophe as bleeding into the spinal canal, both in severity and significance of neural compromise. Certainly, cardiac catheterization involves the placement of a large cannula in a femoral or brachial vessel with subsequent anticoagulation, yet the frequency of neurologic dysfunction is rare. Indeed, single dose and continuous peripheral blocks may represent a suitable alternative to neuraxial techniques in the anticoagulated patient. Communication between clinicians involved in the perioperative management of patients receiving anticoagulants for thromboprophylaxis is essential in order to decrease the risk of serious hemorrhagic complications. Patients should be closely monitored in the perioperative period for early signs of neural compression such as pain, numbness, or weakness. A delay in diagnosis and intervention may lead to irreversible neural ischemia.

INFECTIOUS COMPLICATIONS

Infection can complicate any regional technique, but neurologic sequelae are rare. The infectious source can be exogenous due to contaminated equipment or medication, or endogenous secondary to a bacterial source in the patient seeding to the remote site of needle or catheter insertion. Although infection at the site of needle insertion is an absolute contraindication to regional anesthesia, common sense dictates that encroaching cellulitis, lymphangitis, or erythema would also preclude a regional technique. Indwelling catheters theoretically increase the risk of infectious complications. However, while colonization may occur, infection is rare.[22,23,38–40] Local infections are treated with catheter removal and antibiotics. Retained catheter fragments may be a source of infection.[22] Strict attention to aseptic technique is crucial to reducing regional anesthesia related infections, particularly in the presence of indwelling catheters.[41]

PATIENTS WITH PREEXISTING NEUROLOGIC DISORDERS

Patients with preexisting neurologic disease present a unique challenge to the anesthesiologist. The cause of postoperative deficits is difficult to evaluate, because neural injury may occur as a result of surgical trauma, tourniquet pressure, prolonged labor, improper patient positioning, and/or anesthetic technique. Progressive neurologic diseases may coincidentally worsen perioperatively, independent of the anesthetic method.[42,43] The decision to proceed with a regional anesthesia in these

patients should be made on a case-by-case basis and involves understanding the pathophysiology of neurologic disorders, the mechanisms of neural injury associated with regional anesthesia, and the overall incidence of neurologic complications after regional techniques. If a regional anesthetic is indicated or requested, the patient's preoperative neurologic examination should be formally documented and the patient must be made aware of the possible progression of the underlying disease process.

The presence of preexisting deficits, signifying chronic neural compromise, theoretically places these patients at increased risk for further neurologic injury.[29] It is difficult to define the actual risk of neurologic complications in patients with preexisting neurologic disorders who receive regional anesthesia; no controlled studies have been performed, and accounts of complications have appeared in the literature as individual case reports. In a study examining the effect of local anesthetics on nerve conduction block and injury in diabetic rats, Kalichman and Calcutt[26] reported that the local anesthetic requirement is decreased and the risk of local anesthetic-induced nerve injury is increased in diabetes. Clinically, the success rate of regional techniques is increased in diabetic patients.[44] These findings suggest that diabetic patients may require less local anesthetic to produce anesthesia and that a reduction in dose may be necessary to reduce the risk of neural injury by doses considered safe in nondiabetic patients. However, confirmatory human studies are lacking. Conversely, Hebl et al.[45] noted no difference in neurologic function in patients undergoing ulnar nerve transposition under axillary block versus general anesthesia. However, all patients in the axillary block group with postoperative worsening of neurologic function had an ulnar paresthesia or nerve stimulator response reported during their regional technique.

Patients with preoperative neurologic deficits may undergo further nerve damage more readily from needle or catheter placement, local anesthetic systemic toxicity, and vasopressor-induced neural ischemia. Dilute or less potent local anesthetic solutions should be used when feasible to decrease the risk of local anesthetic toxicity. The use of epinephrine-containing solutions in patients with preexisting neurologic deficits is controversial. The potential risk of vasoconstrictor-induced nerve ischemia must be weighed against the advantages of improved quality and duration of block. Because epinephrine and phenylephrine also prolong the block and therefore neural exposure to local anesthetics, the appropriate concentration and dose of local anesthetic solutions must be thoughtfully considered.[2]

PERFORMANCE OF REGIONAL TECHNIQUES IN ANESTHETIZED PATIENTS

The performance of regional blockade on anesthetized patients theoretically increases the risk of perioperative neurologic complications, since these patients are unable to respond to the pain associated with needle- or catheter-induced paresthesias or intraneural injections. However, there are few data to support these concerns. Cases are typically reported individually; no randomized study or large review has been performed to date.[14,15] There are also medicolegal issues. The actual risk of neurologic complications in patients undergoing regional techniques while anesthetized or heavily sedated has not been formally evaluated. The apparent safety of performing regional techniques under general anesthesia that is demonstrated in the pediatric literature must be carefully interpreted. As previously mentioned, epidemiologic series report direct trauma and toxicity as the etiologies of most neurologic complications, and have identified pain during needle placement or injection of local anesthetic as risk major factors.[1,8,9]

Peripheral and plexus blocks (compared to neuraxial techniques) represent additional risk when performed on an anesthetized patient. The larger dose of local anesthetic given as a single bolus over a relatively short interval increases the risk of systemic toxicity while heavy sedation or general anesthesia diminishes the patient's ability to report early signs of rising local anesthetic blood levels. In addition, although some peripheral techniques are performed as a field block, most require that the nerve or sheath be directly identified by eliciting a paresthesia or nerve stimulator response or by locating an adjacent vascular structure. However, the use of a nerve stimulator does not replace the patient's ability to respond to the pain of needle trauma or intraneural injection. Urmey et al.[46] performed interscalene blocks on unpremedicated patients using the paresthesia technique with insulated (10 patients) and noninsulated (20 patients) needles. Paresthesias were elicited with the nerve stimulator power off. Upon elicitation of the paresthesia, the nerve stimulator was turned on and the amperage slowly increased to a maximum of 1.0 milliamperes. Only 30% of patients exhibited any motor response. There was no correlation between site of paresthesia and associated motor response. These results suggest that since it is possible to have sensory nerve contact and not elicit a motor response, use of a nerve stimulator does not protect the anesthetized patient from nerve injury. Passannante[15] described a case report of spinal anesthesia and permanent brachial plexopathy in a patient who underwent an interscalene block using a nerve stimulator while anesthetized. Motor response in the hand was obtained at 0.2 milliamperes; no blood or CSF was aspirated. It was postulated the needle tip was in a dural sleeve or the subarachnoid space, with a portion of the local anesthetic injected intraneurally. The patient's inability to respond to pain allowed a larger intraneural injection and increased the severity of nerve injury. Benumof[14] reported four cases of permanent cervical spinal cord injury following interscalene

Table 3. EMG Abnormalities After Axonal Injury

Time after injury	Insertional activity	Fibrillation	Recruitment	Amplitude
Acute (<14 d)	Normal	Absent	Reduced	Normal
Subacute (14–21 d)	Increased	Present	Reduced	Normal
1–3 month	Increased	Present	Reduced	May be increased
>6 month	May be increased	Present, but decreased	Reduced	Increased

From Hogan et al. (50). Used with permission.

block performed with the patient under general anesthesia or heavy sedation. In three cases, a nerve stimulator was used to localize the brachial plexus.

DIAGNOSIS AND EVALUATION OF NEUROLOGIC COMPLICATIONS

Neurologic deficits that arise within the first 24 hours most likely represent extra- or intraneural hematoma, intraneural edema, or a lesion involving a sufficient number of nerve fibers to allow immediate diagnosis. However, in many cases of persistent paresthesias after regional anesthesia, the symptoms of nerve injury do not develop immediately after the injury, but have their onset days or weeks later.[10] In a study evaluating nerve conduction after nerve block at the elbow, Löfström et al.[47] observed that while ulnar nerve action potential had returned to normal 24 hours after injection, subsequent examinations at weekly intervals detected abnormally low amplitudes in 3 of 28 subjects, although only 1 complained of neurologic dysfunction. Late disturbances in nerve function have also been reported after human microneurography, a technique involving percutaneous electrical stimulation of a nerve.[48] The presentation of late disturbances in nerve function suggests an alternative etiology such as tissue reaction or scar formation, although it is not possible with the existing data to determine whether this reaction is due to mechanical trauma, chemical trauma, or both.

Although most neurologic complications resolve completely within several days or weeks, significant neural injuries necessitate neurologic consultation to document the degree of involvement and coordinate further work-up. Neurophysiologic testing, such as nerve conduction studies, evoked potentials, and electromyography are often useful in establishing a diagnosis and prognosis.[49,50] A reduced amplitude in evoked responses indicates axonal loss, while increased latency occurs in the presence of demyelination. Fibrillation potentials are present during active axonal degeneration. They appear 2–3 weeks after injury and are maximal at 1–3 months (Table 3). Because of the decreased number of axons present in patients with neurologic conditions, there is a reduction in neuron recruitment during voluntary effort. The degree of reduction parallels the severity of the disorder. Despite many applications, nerve conduction studies have several limitations. Typically only the large sensory and motor nerve fibers are evaluated; dysfunction of small unmyelinated fibers would not be detected. In addition, abnormalities will not be noted on EMG immediately after injury, but rather require several weeks to evolve. Although it is often recommended to wait until evidence of denervation has appeared before performing neurophysiologic testing, a baseline study (including evaluation of the contralateral extremity) would be helpful in ruling out underlying pathology or a preexisting condition.

In conclusion, major complications after regional anesthetic techniques are rare, but can be devastating to the patient and the anesthesiologist. Prevention and management begin during the preoperative visit with a careful evaluation of the patient's medical history and appropriate preoperative discussion of the risks and benefits of the available anesthetic techniques. Alternative anesthetic techniques such as peripheral blocks or general anesthesia should be considered for patients at increased risk for neurologic complications following neuraxial block. The decision to perform a regional anesthetic technique on an anesthetized patient must be made with care since these patients are unable to report pain on needle placement or injection of local anesthetic. Efforts should also be made to decrease neural injury in the operating room through careful patient positioning. Postoperatively, patients must be followed closely to detect potentially treatable sources of neurologic injury, including hematoma or abscess, constrictive dressings, improperly applied casts, and increased pressure on neurologically vulnerable sites. New neurologic deficits should be evaluated promptly by a neurologist, or neurosurgeon, to document formally the patient's evolving neurologic status, arrange further testing or intervention, and provide long-term follow-up.

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The Role of the Anesthesiologist in Fast-Track Surgery

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Surgical injury may be followed by pain, nausea and vomiting, ileus, stress-induced organ dysfunction (pulmonary, cerebral, cardiovascular), fatigue and catabolism, all of which may contribute to morbidity, need for hospitalization and delayed convalescence. Since the postoperative recovery process includes multiple pathogenic factors, an enhanced postoperative recovery program (the concept of fast-track surgery) requires a stepwise multimodal, evidence-based intervention. The concept was introduced a decade ago[1] and subsequently has been demonstrated to provide a powerful instrument to enhance recovery, reducing morbidity, hospital stay, and convalescence across several surgical procedures, ranging from simple day-case procedures to more complex procedures, such as colorectal surgery, aortic aneurisms, hip fracture surgery, etc.[2–4]

T1 In Table 1, some of the factors to be considered when organizing a fast-track surgical program are listed. Obviously, the fast-track methodology requires an interdisciplinary approach including the patient, the anesthesiologist, the surgeon and the surgical nurses, nutritional support, physiotherapy, etc. As seen in Table 1, the anesthesiologist plays a key role in several areas to secure a successful fast-track program.[2,3] The present paper is a short update on recent achievements of interest to the anesthesiologist when participating in multimodal rehabilitation programs, and where the reader is referred to a recent extensive
F2 review covering the literature up to 2007.[3] In Figure 1, the basic principles of the fast-track methodology is shown, and the discussion will be focused on pre-, intra-, and postoperative factors of interest for the anesthesiologist.

Preoperatively

There has been an increased recent focus on pre- and early intraoperative optimization of fluid status, and where it is now well established in outpatient and short stay procedures that more than 1–1.5 l of crystalloids is required for an enhanced recovery.[3–5] Optimal fluid management should be structured on a procedure-specific basis, since each procedure may have different fluid dynamics.[6] In addition, the concept of goal-directed fluid therapy has proven valid across several major procedures[7,8] and is based on an individualized optimization of stroke volume, which is different from previous cardiovascular optimization regimens aiming at general well-defined goals, but not considering the large inter-individual variability in cardiovascular performance. Future studies on the goal-directed fluid management concept are required to outline indications and results in individual procedures and patient groups.

The classical concept of preoperative bowel clearance in major abdominal procedures has been questioned, and several randomized trials have shown it to be unnecessary or even shown to increase morbidity, especially in colorectal procedures.[9,10] The consequences are important for the anesthesiologist since preoperative bowel clearance may result in a variable degree of hypovolemia, thereby hindering optimal clinical judgment of fluid balance unless a goal-directed approach is utilized. Base on experimental studies, the concept of a preoperative carbohydrate load has been introduced.[11] Although the anti-catabolic effects are well-documented,[11] the overall clinical outcome effects in minor and major procedures need to be defined before general recommendations.[12–14]

Intraoperatively

The importance of temperature control, local regional and central neuraxial blockades, and monitored anesthesia care has been covered in detail.[3] Among the regional anesthetic/analgesic techniques, the intraoperative use of high-volume infiltration anesthesia regimens in hip and knee replacement has so far shown extremely promising results with improved and prolonged analgesia, allowing early mobilization and shortening hospital stay.[15,16] These techniques should receive further attention and be compared to the otherwise well-documented effective continuous peripheral nerve block techniques,[3] since the high-volume infiltration technique may be easier and less demanding on expertise. Furthermore, it may be combined with a continuous wound infusion analgesic technique.[17]

The effect of the amount of *intra*operative crystalloid combined with a fast-track methodology has been assessed in three recent blinded randomized trials in cholecystectomy, colonic surgery, and knee replacement,[18–20] confirming that >1 L Ringer lactate is required for optimizing perioperative pathophysiology and functional recovery in outpatient laparoscopic cholecystectomy,[18] while there may be little differences in functional recovery in knee replacement when receiving an amount between 2.5 and 5 L Ringer lactate.[19] In contrast, in colonic surgery[20] an intraoperative amount of 2 L Ringer lactate may have a

Table 1. Why is the Postoperative Patient in Hospital Today?

	Factors where anesthesiologists play a key role
Organ dysfunction ("surgical stress")	*
Hypothermia-induced organ dysfunction	*
Pain, nausea, vomiting and ileus	*
Organ dysfunction due to fluid excess/hypovolemia	*
Hypoxemia – sleep disturbances	*
Immobilization-induced organ dysfunction	†
Semi-starvation-induced organ dysfunction	†
Fatigue	
Traditional care principles (tubes, drains, catheters, monitoring, restrictions, etc.)	
Surgical complications	

* = yes.

† = important contribution to facilitate mobilization and oral nutrition.

potential risk of increasing morbidity and that probably about 2.5 to 3 L should be given to prevent hypovolemia.[20] Further procedure-specific studies on the optimal amount of crystalloid combined with the goal-directed approach[7,8] and the fast-track methodology are required, and also to evaluate the need for concomitant colloid administration. The role of the anesthesiologist to reduce nausea, vomiting, and paralytic ileus is well established.[2–4,21]

Postoperatively

Recent developments in multimodal, non-opioid analgesia to enhance recovery has been covered before.[3] There is an important need for the anesthesiologists to change their strategy when integrating optimized perioperative pain management into postoperative outcome studies.[22,23] Thus, most outcome studies in relation to analgesic techniques have not considered other aspects of perioperative care such as the fast-track methodology and thereby not utilizing the advantageous physiological effect of the different non-opioid pain regimens.[22,23] The time has therefore come for an optimized design of pain-outcome studies[23] as has been introduced in the published fast-track studies.[2–4]

Although the concept of multimodal analgesia was launched about 15 years ago[24] and subsequently confirmed in several studies,[3] there is a need for studies including *several* non-opioid analgesics. Thus, inclusion of gabapentanoids[25] and glucocorticoids[26] should be studied when combined with other non-opioid analgesics. Such studies, performed on a procedure-specific basis, should also include appropriate local anesthetic techniques, and where continuous wound infusion of local anesthetics[17] or IV local anesthetics[27,28] may be considered to provide improved analgesia, thereby to facilitate recovery in fast-track clinical pathways. The role of the anesthesiologist in this process is self-evident.

Organizational Issues

Although much evidence has been available from large consecutive cohort series or randomized trials on the results of a multimodal rehabilitation effort within the fast-track methodology,[2–4] widespread implementation into clinical practice has been relatively slow. Thus, several series have documented an apparent reluctance to implement the scientific evidence,[29–33] calling for an intensified multidisciplinary collaboration between anesthesiologists, surgeons, and surgical nurses. Although many factors are involved in the translation of documented scientific evidence to clinical practice,[34,35] the documented major improvements in outcome by the fast-track methodology hopefully will bring anesthesiologists and surgeons together to achieve these advantages.

Future Strategies for the Anesthesiologist to Enhance Fast-Track Surgery

The role of the anesthesiologist in perioperative medicine is well established and should expand outside the operating room into the surgical ward and also into the postdischarge period. Such strategies may include an increased use and investigation of multipharmacological modification of stress responses during and after surgery,[36–38] participation in postoperative rounds by anesthesiologists in certain high-risk patient populations, i.e., hip fracture,[39] participation in and leading the introduction and investigation of "outreach" services or early identification and treatment of postoperative organ dysfunction[40,41] and participation in multidisciplinary collaboration to identify patients at risk for persistent postsurgical pain and possibilities for early intervention.[42]

CONCLUSIONS

As is apparent from this short updated review on recent developments combined with a previous extensive review,[3] the anesthesiologist plays an increasingly important role in the process to enhance postoperative recovery and reducing morbidity. This especially applies to development and documentation of well-defined procedure-specific care programs within the fast-track methodology. Future advances in fast-track surgery will require a close interdisciplinary collaboration within anesthesia, pain management, surgery, and nursing care. The focus should go beyond the surgical procedure to expand to the surgical ward and the postdischarge period to implement and develop techniques to improve analgesia and limit organ dysfunctions. The major improvements in outcome documented in the fast-track surgical literature hopefully will stimulate this collaboration. In this process, interdisciplinary participation in scientific meetings and symposia will be helpful where anesthesiologists and surgeons are contributing on procedure-specific topics. The future is now to develop, establish, and implement the evidence.

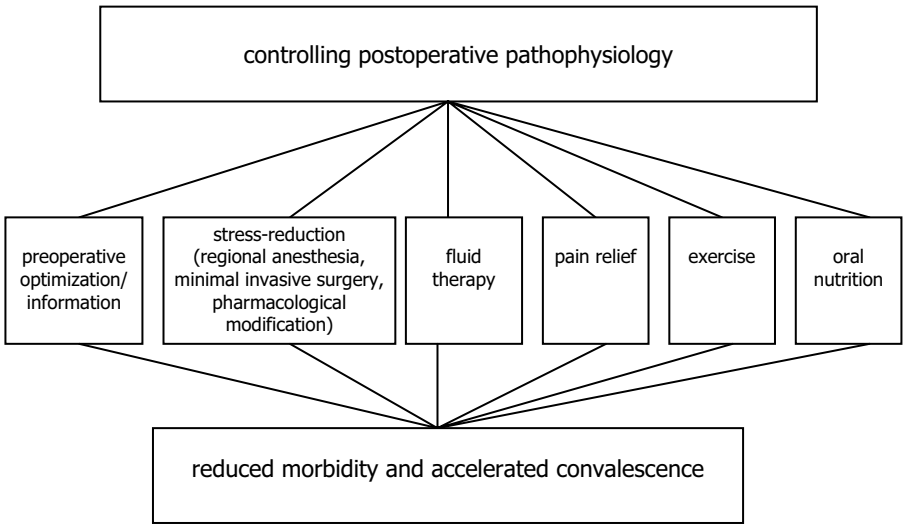

Figure 1. •••.

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Antiplatelets to Anticoagulants: Making Sense of the Coagulation Cocktails

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Anticoagulation is the cornerstone of therapy in patients with ischemic cardiovascular disease. In patients who develop 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[1,2] Activation and expression of the glycoprotein IIb/IIIa receptor (where fibrinogen binds) on platelets leads platelet aggregation and, thrombus formation.[2] 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-Plavix), and the glycoprotein IIb/IIIa inhibitors, reduce adverse events that are associated with plaque rupture.[3] Fibrinolytic agents are infrequently used in the current era with all of the available catheter and pharmacologic agents available. As a result, patients often present for surgery with underlying hemostatic disorders because of preexisting preoperative anticoagulation or antiplatelet therapy.[4] 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.[5,6]

Under normal circumstances, there is a complex and delicate equilibrium between blood cells, platelets, coagulation factors, natural inhibitors of coagulation, and the fibrinolytic system.[7] Surgical patients also develop additional acquired hemostatic alterations that contribute to postoperative bleeding, causes that include activation of the coagulation, fibrinolytic, and inflammatory pathways.[8] Even healthy patients can develop massive hemorrhage and/or tissue injury following trauma, surgery, or in an obstetrical population.[9] Hemostasis is also a far more complex system than intrinsic and extrinsic hemostatic activation as taught in medical school.[10,11] 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.[11–14] The increasing use of low-molecular weight heparins (LMWH), heparinoids (Orgaran), pentasaccharide (fondaparinux), oral anticoagulants (warfarin and new oral anti-Xa inhibitors), platelet inhibitors (thienopyridines-clopidogrel or IIb/IIIa receptor antagonists), or direct thrombin inhibitors (r-hirudin, bivalirudin, argatroban), also may potentiate bleeding.[15,16] This review will focus on current pharmacologic therapies surgical patients may receive and therapeutic prohemostatic pharmacologic approaches that are used to treat or prevent bleeding.

ANTICOAGULATION: HEPARIN, DERIVATIVES, AND THROMBIN INHIBITORS

Anticoagulation is based on inhibiting both thrombin activation and platelet activation.[16–19] Thrombin is a potent procoagulant that generates fibrin from soluble fibrinogen, activating factors V and VIII, and activating platelets.[11] Activated platelets adhere to injured vascular endothelia, express IIb/IIIa receptors, aggregate, and further enhance generation of thrombin.[20] Because of the complex humoral amplification system linking both hemostatic and inflammatory responses, there are multiple pathways to produce thrombin and prothrombotic effects.[5] 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 enhance 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 either porcine intestine or from beef lung where it is stored in the mast cell granules. Heparin is an acidic polysaccharide, with sulfate groups important in its anticoagulant activity. Unfractionated heparin is a heterogeneous mixture of 3000 to 30,000 Dalton fragments.[21] Heparin binds to antithrombin III (antithrombin or AT III) increasing the rate of thrombin-AT III complex formation, but also

inhibits other steps in coagulation, through acceleration of the reactions between antithrombin and thrombin or factor Xa.[21] One of the advantages of heparin anticoagulation is that it can be reversed immediately by removing heparin from AT III with protamine.[22] Unfractionated heparin is also an important cause of heparin induced thrombocytopenia.

LOW-MOLECULAR-WEIGHT HEPARINS (LMWH)

Like unfractionated heparin, low-molecular-weight heparins are glycosaminoglycans.[18] Low-molecular-weight heparins are fragments of unfractionated heparin purified to a mean molecular weight of about 5000.[18] Low-molecular-weight heparins have a longer half-life, and dose-independent clearance; the recovery of antifactor Xa activity approaches 100 percent, compared with about 30% with unfractionated heparin. The plasma half-life of low-molecular-weight heparins is longer than unfractionated heparin, ranging 2–4 hours after IV injection, and 3–6 hours after subcutaneous injection.[18]

SYNTHETIC Xa INHIBITORS (FONDAPARINUX AND DANAPAROID)

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. Danaparoid is also a synthetic agent that, although approved for use in the United States, is not currently available and is used in Europe for treating heparin induced thrombocytopenia (HIT).

ORAL ANTICOAGULANTS

Vitamin K antagonists (VKAs) (e.g., warfarin) are the only oral anticoagulants currently available for clinical use. These agents inhibit II, VII, IX and X, key components of the hemostatic cascade, but also inhibit protein C and S. Warfarin has major limitations, including slow onset and offset, a narrow therapeutic window, and metabolism affected by diet, concomitant drugs, and genetic polymorphisms and requires careful monitoring.[23] Ximelgatran was the first oral anticoagulant, but was not approved in the United States because of organ toxicity. Rivaroxaban and apixiban are new oral anticoagulants in advanced stages of clinical development that are directed against the active site of factor Xa or thrombin, the enzymes responsible for thrombin generation and fibrin formation, respectively.[23] Rivaroxaban and apixiban target factor Xa, whereas dabigatran etexilate inhibits thrombin. Rivaroxaban is a small molecule directed against the active site of factor Xa. After oral administration, it is absorbed in the stomach and small intestine with a bioavailability of 60% to 80%. Peak plasma levels are achieved in 3 hours, and the drug circulates with a half-life of 9 hours.[23] Ximelagatran is an oral anticoagulant that has recently been withdrawn in Europe.

HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

Heparin-induced thrombocytopenia (HIT) is a serious, yet treatable, prothrombotic disease that develops in 1% to 3% of heparin-treated patients and dramatically increases their risk of thrombosis.[24] The antibodies that mediate HIT, i.e., heparin-platelet factor 4 antibodies, occur more frequently than the overt disease itself and, even in the absence of thrombocytopenia, are associated with increased thrombotic morbidity and mortality.[24] HIT should be suspected whenever the platelet count drops >50% from baseline after starting heparin (or sooner if there was prior heparin exposure) and/or new thrombosis occurs during, or soon after, heparin treatment, with other causes excluded. When HIT is strongly suspected, with or without complicating thrombosis, heparins should be discontinued and a fast-acting, non heparin alternative anticoagulant such as a direct thrombin inhibitor (argatroban or r-hirudin), or danaparoid should be initiated immediately.[24,25]

Even without inducing thrombocytopenia, heparin-PF4 antibodies are clinically important, increasing morbidity or mortality in various patient populations. In patients with, versus without, heparin-PF4 antibodies, irrespective of platelet count, there are significant increases in the length of hospitalization and in-hospital mortality after cardiac surgery[26] and postoperatively in orthopedic surgery patients. Despite their association with long-term adverse effects, circulating heparin-PF4 antibodies are transient. For cardiac surgery, bivalirudin has emerged as the agent most studied in this setting, for on or off pump surgery.[27,28] However, HIT is a prothrombotic disease that carries significant morbidity and mortality and requires immediate therapy.[24] The agents approved for use in HIT are the direct thrombin inhibitors and danaparoid based on current recommendations.[25]

PLATELET INHIBITORS

In patients with myocardial ischemia and or atherosclerotic vascular disease, inhibiting platelet activation is the cornerstone of therapy.[29] Platelet inhibitors/antiplatelet agents should also be considered as anticoagulants, and potentially place the patient at risk 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.[30] 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.[31] More potent antiplatelet agents include clopidogrel (Plavix) and IIb/IIIa receptor antagonists (abiximab, tirofiban, eptifibatide). Clopidogrel is more potent than aspirin, and inhibits 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.[30,32,33] 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.[29]

Vincenzi noted a 45% complication rate and a mortality of 20% reported in patients undergoing noncardiac surgery after coronary artery stenting.[34] 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% suffered 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.[34] 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.

PROCOAGULANT AGENTS

Anesthesiologists are frequently 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 are reviewed. Therefore, clinicians must understand some of the potential procoagulant therapies available to reverse bleeding or anticoagulation therapy.[35] These agents include antifibrinolytics, protamine, desmopressin, fibrinogen, purified protein concentrates, recombinant factor VIIa [rFVIIa]), and topical hemostatic agents, and each will be considered separately.

APROTININ

Aprotinin is a broad-spectrum serine protease inhibitor that inhibits factor XII, kallikrein, plasmin, and PAR1 receptors.[36] In cardiac surgery, multiple randomized, placebo-controlled trials on aprotinin safety and efficacy have demonstrated that aprotinin therapy reduces bleeding (i.e., mediastinal and chest tube drainage) and decreases the need for allogeneic transfusion, and the proportion of patients needing transfusion of allogeneic blood.[37,38] Sedrakyan reported data from 35 CABG trials (n = 3879) confirming that aprotinin reduces transfusion requirements (relative risk 0.61) relative to placebo, with a 39% risk reduction, and was not associated with increased or decreased mortality (relative risk 0.96), myocardial infarction (relative risk 0.85), or renal failure (relative risk 1.01) risk, but it was associated with a reduced risk of stroke (relative risk 0.53). Aprotinin's mechanism of action is complex and may also involve reduction of the inflammatory response.[39] Aprotinin has also been studied in clinical trials in vascular, liver transplantation,[40] and orthopedic surgery.[41]

Over the past 2 years, two articles were published from observational databases that questioned the safety of aprotinin.[42,43] In response to these articles, and to an additional observational study called the i3 Drug Safety study, the United State's Food and Drug Administration (FDA) conducted two meetings to review the risk/benefit profile of Trasylol® (aprotinin injection) to reduce bleeding in coronary artery bypass graft (CABG) surgery, information that can be found at the FDA web site www.FDA.gov. On October 19, 2007, FDA was notified of a Data Safety Monitoring Board's (DSMB) recommendation to stop patient enrollment in an independent Canadian study, the aprotinin treatment group arm of the Blood conservation using antifibrinolytics: A randomized trial in a cardiac surgery population (BART) study. The preliminary findings suggest that, compared to the antifibrinolytic drugs, ε-aminocaproic acid and tranexamic acid, aprotinin increases the risk of death (http://www.fda.gov/cder/drug/early_comm/aprotinin.htm). The BART study was designed to test the hypothesis that aprotinin was superior to ε-aminocaproic acid and tranexamic acid in decreasing the occurrence of massive bleeding associated with cardiac surgery. The study had planned to enroll approximately 3,000 adult Canadian patients who were to undergo various types of cardiac surgery that placed them at high risk for bleeding. Information from the interim analyses performed by the DSMB is limited, but FDA has been informed of the following: the 30-day mortality in the aprotinin group nearly had reached conventional statistical significance at the interim analysis, when compared to either ε-aminocaproic acid or tranexamic acid; a trend toward increased mortality in the aprotinin group had been observed throughout the study; the use of aprotinin was associated with less serious bleeding than either of the comparator drugs; however, more deaths due to hemorrhage had been observed among patients receiving aprotinin; the DSMB concluded that continued enrollment of patients into the aprotinin group was unlikely to significantly change the study findings.

The FDA noted that "additional data collection and analyses must be performed to more thoroughly assess the findings from the BART study." On November 5, 2007, the FDA announced that, at the agency's request, Bayer Pharmaceuticals Corporation had agreed to a marketing suspension of aprotinin (Trasylol) a drug used to control bleeding during heart surgery, pending detailed review of preliminary results from a Canadian study that suggested an increased risk for death ((http://www.fda.gov/bbs/topics/NEWS/2007/NEW01738.html). They noted the "FDA requested the suspension in the interest of patient safety based on the serious nature of the outcomes suggested in the preliminary data. FDA has not yet received full study data but expects to act quickly with Bayer, the study's researchers at the Ottawa Health Research Institute, and other regulatory agencies to undertake a thorough analysis of data to better understand the risks and benefits of Trasylol. There are not many treatment options for patients at risk for excessive bleeding during cardiac surgery. Thus, FDA is working with Bayer to phase Trasylol out of the marketplace in a way that does not cause shortages of other drugs used for this purpose. Until FDA can review the data from the terminated study it is not possible to determine and identify a population of patients undergoing cardiac surgery for which the benefits of Trasylol outweigh the risks. Understanding that individual doctors may identify specific cases where benefit outweighs risk, FDA is committed to exploring ways for those doctors to have continued, limited access to Trasylol."

ANTIFIBRINOLYTIC AGENTS: EPSILON-AMINOCAPROIC ACID (EACA) AND TRANEXAMIC ACID (TXA)

The two synthetic antifibrinolytic agents currently available include the lysine analogs EACA and TXA that competitively inhibits 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. Tranexamic acid also directly inhibits plasmin, but higher doses are required than are needed to reduce plasmin formation.[35,44] 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. we reported a study of 100 patients undergoing CABG surgery, and noted that EACA significantly reduced chest tube drainage by 30% compared to the placebo group (EACA, 650[4] 261 mL; placebo, 940 $\pm$ 627 mL; $P = 0.003$); however, it did not reduce the need for allogeneic blood transfusion.[45] Although meta-analyses of patients undergoing cardiac surgery suggests that lysine analogs decrease transfusion requirements and the rate of surgical reexploration from 4.7 to 1.9% (RR, 0.44; 95% CI; 0.22–0.90), these are not consistent finding.[46] In the Cochrane database, 18 trials of TXA (1,342 patients show a reduction in the RBC transfusion rate by a relative 34% (RR, 0.66; 95% CI; 0.54–0.81).[47] while there were only 4 trials of EACA (208 patients that do not demonstrate a reduction in transfusions (RR, 0.48; 95% CI; 0.19–1.19).[47]

PROTAMINE

Protamine is the only available therapeutic approach to reverse unfractionated heparin. Protamine is a polypeptide composed of approximately 70% arginine residues, and thus has a high pKa to reverse the acidic molecule heparin by forming a simple acid-base interaction.[48] Protamine and does not reverse low-molecular-weight heparin. Following administration, protamine rapid reverses heparin as noted by return of activated clotting times, but also with marked elevations plasma concentrations of prothrombin fragment 1.2, thrombin-antithrombin III complex, and fibrin monomer.[49] Protamine can cause adverse reactions including anaphylaxis, acute pulmonary vasoconstriction and right ventricular failure, and hypotension.[48] Patients with diabetes are at an increased risk for adverse reactions due to the presence of neutral protamine Hagedorn (NPH), which contains insulin and protamine, causing increased protamine sensitization.[48,50,51] Individuals reported at risk for protamine reactions include patients with vasectomy, multiple drug allergies, and prior protamine exposure.[52]

DESMOPRESSIN

Desmopressin (DDAVP) is the V2 analog of arginine vasopressin that stimulates the release of ultra large von Willebrand factor (vWF) multimers from endothelial cells.[4,53–55] 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.[53,54] Surgical patients who might benefit from use of DDAVP are not clear. DDAVP is administered IV at a dose of 0.3 mg/kg, and should be given over 15–30 minutes to avoid hypotension.[56,57,58] Most studies have not confirmed the initial reported efficacy during complex cardiac surgery.[56,58–61] 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).[4,62]

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).[44,63] Recombinant activated factor VIIa (rFVIIa; NovoSeven®, Novo Nordisk) is approved for hemophilia patients with inhibitors to treat bleeding. Currently, rFVIIa is increasingly used off label as a universal prohemostatic agent in complex clinical situations for life threatening hemorrhage.[64]

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.[12] TF is a membrane-bound glycoprotein that is expressed on subendothelial cells after tissue injury and loss of endothelial protective mechanisms.[65] Circulating FVIIa accounts for nearly 1% of circulating FVII, and is inactive until bound with TF.[12] 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.[13] 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.[66] Multiple publications report rFVIIa in surgical patients and cardiac surgical patients including a recent reported analysis of the clinical studies.[64,67,68] 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.[69] Additional studies are needed to further evaluate dosing, safety and efficacy in perioperative use of rFVIIa. However, guidelines as reported by Goodnough[69] and Despotis[70] for off label use in patients with life threatening hemorrhages.

Controlled clinical trials report the incidence of thrombotic complications among patients who received rFVIIa was relatively low and similar to that among patients who received placebo.[67] However, most case reports administering rFVIIa as rescue therapy include patients who have impaired coagulation, have received multiple transfusions, and are at a high risk for adverse events. The complex role that transfusion therapy has in producing adverse outcomes is increasingly being noted in the literature[71,72] A report using the FDA MED Watch database noted thromboembolic events in patients with diseases other than hemophilia in whom rFVIIa was used off-label basis, and included 54% of the events as arterial thrombosis (e.g., stroke or acute myocardial infarction).[73] Venous thromboembolism (mostly, venous thrombosis or pulmonary embolism) occurred in 56% of patients. In 72% of the 50 reported deaths, thromboembolism was considered the probable cause. It is not clear to what extent the clinical conditions requiring the use of rFVIIa may have contributed to the risk of thrombosis.[4] Other major issues regarding rFVIIa include costs and dosing. Currently, randomized clinical trials are underway to study this agent in various surgical patients. This drug has also seen widespread use in battlefield conditions in Iraq.

REVERSAL OF VITAMIN K ANTAGONISTS ASSOCIATED COAGULOPATHY

Prohemostatic agents are often required 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[74] 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[75] 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.[76–78] Although there are historical concerns regarding potential thrombotic risk with PCCs, present-day PCCs are much improved.[78] Clinical data suggest that rFVIIa may provide similar benefits over FFP as PCCs; however, preclinical comparisons suggest that PCCs are more effective in correcting coagulopathy.[78] PCC are being investigated as a therapeutic option in this setting.

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. Gelatin sponges or Gelfoam® are comprised of purified pork skin gelatin that increases contact activation to help create topical clot. Oxidized regenerated cellulose is also known as Surgicel or Oxycel that works like Gelfoam. Microfibrillar collagen is Avitene®, and is collagen, which is derived from bovine skin. Collagen sponges, these come in a wide variety of different commercial forms, and are derived from bovine Achilles tendon or bovine skin. One of the widely used agents is topical thrombin. Floseal™ is bovine thrombin plus cross-linked gelatin granules mixed together. The problem with bovine thrombin is that antibodies form to this molecule and its contaminant proteins may contribute to hypersensitivity and coagulopathy due to antibody formation.[79] As a result, there are now purified human thrombin (purified from multiple donors) and just recently approved by the FDA a recombinant thrombin for RECOTHROM™ (http://www.zymogenetics.com/products/documents/RECOTHROM_Prescribing_Info.pdf).

THE FUTURE

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

Suggested web sites: Bleedingweb.com, HeparinInducedThrombocytopenia.com

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Problems and Pitfalls in Pediatric Anesthesia

Linda J. Mason, MD

ANESTHESIA-RELATED CARDIAC ARREST IN THE PEDIATRIC PATIENT

The etiology of cardiac arrest in the pediatric patient has changed over the past 20 years as practice has evolved in the care of these patients. The Pediatric Closed Claims Study in 1993 showed respiratory events were the most common category accounting for 43% of claims with inadequate ventilation seen in half of the respiratory events. The typical profile in this category of inadequate ventilation were healthy, nonobese children breathing halothane spontaneously whose arrest was preceded by hypotension or bradycardia. These children were difficult to resuscitate successfully, 70% died and 30% had permanent central nervous system impairment. Pulse oximetry was used in 7% of the Closed Claim cases and capnometry in 5%.[1] Recently the Pediatric Perioperative Cardiac Arrest (POCA) Registry has provided some new data. Out of 1,089,200 anesthetics, there were 150 cardiac arrests which were deemed anesthesia related (1.4/10,000).[2] Several points are relevant in analysis of this data.

First, an increased incidence of cardiovascular causes (32%) have differed from the Pediatric Closed Claims Study in 1993 where only 13% were from cardiovascular causes. This may have some basis in the fact that using chest compression was necessary as entry criteria for the POCA Registry or the fact that the use of pulse oximetry in 98% and capnography in 86% of cases may be more effective in preventing respiratory than cardiovascular incidents before arrests occur. Most of the cardiac arrests (82%) occurred during induction or maintenance of anesthesia. Bradycardia (54%), hypotension (49%), abnormality of Spo_2 (46%) or inability to measure blood pressure (25%) were the most common antecedent events. Twenty-one percent of arrests occurred during emergency surgery.

Second, infants are at increased risk. Infants <1-year accounted for 55% of the anesthesia related cardiac arrests. Several pediatric studies have confirmed that infants <1-year have the highest anesthetic risk and that mortality is inversely proportional to age with the highest risk in the <1 month of age group. This may be notably related to a higher ASA Physical Status (PS) Classification with underlying patient disease (particularly congenital heart disease) but also to cardiovascular depression by inhalational agents. In infants <30 days of age the MAC of halothane is 0.87%, as compared with children 1–6 months of age - MAC of 1.08%. With isoflurane, the MAC for preterm infants (<32 weeks) is 1.28%, 32–37 weeks is 1.41%, and for term (0–1 month) 1.60%, with 1–6 months being 1.87%. Only sevoflurane appears to be different with the MAC being constant at 3.2%–3.3% for neonates and infants <1 month, decreasing to 3% at 1–6 months, and 2.5&-2.8% for 7 months–12 years.[3]

Recent studies show sevoflurane may be less of a myocardial depressant and have less potential for producing bradycardia than halothane in infants.[4] Sevoflurane may also be safer for use in children with congenital heart disease. In comparison with children receiving halothane, the halothane treated patients experienced twice as many episodes of severe hypotension as those who received sevoflurane. Recurrences of hypotension occurred despite increased vasopressor use in the halothane as compared to the sevoflurane treated patients. Risk of hypotension was increased in children <1 year of age compared with older children and patients with preoperative cyanosis had a higher incidence of developing severe desaturation with halothane. Thus sevoflurane may have hemodynamic advantages over halothane in infants and children with congenital heart disease.[5]

Third, 33% of all anesthesia related cardiac arrests occurred in previously healthy ASA PS 1 and 2 patients – mostly medication-related errors (64%). Fifty percent of the arrests caused by halothane cardiovascular depression were seen at inspired concentrations of 2% or less with the median age being 6 months. Controlled ventilation may accelerate the rise in halothane concentration compounded by prolonged exposure due to difficult IV access. Four cases of arrest occurred following probable intravascular injection of local anesthetics. These occurred during combined halothane and caudal anesthesia with injection of 0.25% bupivacaine with 1/200,000 epinephrine despite negative test dose and aspiration. They occurred when both needles and catheters were used to deliver the medication. All had ventricular arrhythmias but were successfully resuscitated without injury.

Mortality rate in ASA PS 3–5 patients was 37% compared to 4% in ASA PS 1–2 patients. ASA PS 3–5 was the strongest predictor of mortality followed by emergency status. Overall the mortality rate in all arrests was 26%.[2]

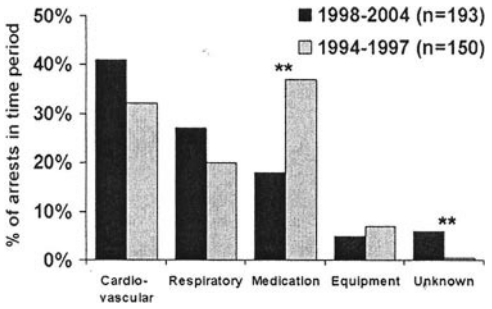

Figure 1. Cause of arrest: Causes of anesthesia-related cardiac arrest in 1998–2004 compared to 1994–1997. Data from 1994 to 1997 previously published and used with permission (Morray, et al. Anesthesiology 2000;93:6–14, © Lippincott Williams & Wilkins). Multiple and miscellaneous other causes (3% 1998–2004 vs 4% 1994–1997) not shown. $^{**}P < 0.01$, 1998–2004 vs 1994–1997 by Z test.

Since publication of the initial series 397 additional cases have been submitted to the POCA Registry and 49% of these arrests were related to anesthetic causes. In the data from 1998–2004, the profile has changed again (Fig. 1). Medication related causes have declined from 37% to 18% of the total due to the decline of cases of cardiovascular depression from inhaled agents, possibly due to the change from halothane to sevoflurane use. Respiratory causes have increased from 20% to 27% the most frequent etiology being laryngospasm. Cardiovascular causes of arrest increased from 32 to 41%. Hypovolemia (often from hemorrhage in spine fusion or craniectomy/craniotomy), the metabolic consequences of massive transfusion (usually hyperkalemia) or hyperkalemia from succinylcholine use were the most frequent known cause of arrest in this category. The exact cause of arrest could not be determined in some cases in the cardiovascular category – frequently these were children with congenital heart disease and an ASA physical status 3–5. Equipment problems (mainly complications from central venous catheter placement) have stayed fairly constant as a cause of arrest in pediatric patients being 7% in 1994–97 and 5% in the 1998–2004 data.

The demographic profile since 1998 has also changed, the percentage of ASA physical status 1 and 2 decreased from 33% to 25% and the percentage of patients <1 year of age decreased from 56 to 38% (Table 1). This may be due to a decreased incidence in the number of arrests reported due to inhalational agents. These arrests were more likely to occur in ASA physical status one or two patients who were <1 year of age. The mortality rate in the two time periods hasn't changed, being 26 and 28%, respectively.[6]

Another study evaluating the data in 92,881 patients from a tertiary care referral center between 1998–2005 indicated the incidence of anesthesia-related cardiac arrest was 0.65/10,000 anesthetics (less than the original POCA data). Both cardiac arrest incidence and mortality were highest among neonates (0–30 days of life) undergoing cardiac procedures. Most patients who experienced perioperative cardiac arrest (88%) had underlying congenital heart disease.[7]

Table 1. Patient Characteristics in Anesthesia-Related Arrests

	1998–2004 $n = 93$	1994–1997[a] $n = 150$
ASA physical status[b]		
1	13 (7)*	23 (15)*
2	34 (18)	27 (18)
3	79 (42)	56 (37)
4	53 (28)	41 (27)
5	11 (6)	3 (2)
Emergency age	40 (21)	31 (21)
<1 mo	21 (11)	22 (15)
1–5 mo	41 (21)	42 (28)
6–11 mo	12 (6)*	19 (13)*
12 mo–5 yr	58 (30)	47 (31)
6–18 yr	60 (31)+	20 (13)+

Percentages in parentheses may not sum to 100% due to rounding.

ASA = American Society of Anesthesiologists.

[a] Previously published data used with permission (Morray et al. Anesthesiology 2000;93:6-14, © Lippincott Williams & Wilkins).

[b] Cases with missing data excluded.

* $P < 0.05$ 1998-2004 vs 1994-1997 by Z-test.

+ $P < 0.01$ 1998-2004 vs 1994-1997 by Z-test.

Used with permission from Bhananker SM, Ramamoorthy C, Geiduschek JM, et al. Anesthesia-related cardiac arrest in children: update from the pediatric perioperative cardiac arrest registry. Anesth Analg 2007;105:344-50.

In another report, the frequency of anesthesia-related cardiac arrests in patients with congenital heart disease undergoing cardiac surgery was 27.1/10,000 anesthetics with no mortality. Cardiac arrest was highest in the neonates.[8] In a Brazilian tertiary care hospital with 53,718 anesthetics over a 9-year period the incidence of anesthesia-related cardiac arrest was 3.35/10,000 and anesthesia-related deaths 0.56/10,000. Major causes of cardiac arrest were airway management and medication administration errors. Major risk factors were neonates and children <1 year (prematurity and congenital heart disease were also factors) and emergency surgery.[9] A final study from an academic pediatric medical center looking at 105,436 procedures (except cardiac catheterization) over a 5-year period reported an incidence of 2.67/10,000 cases. Risk factors included ASA physical status ≥3 and children <1 year of age. Those providers that spent ≤40% of time in the OR also indicated a risk factor.[10]

CLASSIFICATIONS OF CARDIAC ARRESTS

Cardiac Disease

Although most patients who present with a previously undiagnosed heart murmur do not have significant pathology, some do have anatomic disease. Lesions that are implicated with problems during anesthesia are those that include the diagnosis of pulmonary hypertension, hypoplastic arteries and ventricles and left to right shunts. Murmurs should be characterized prior to surgery – especially in infants. A history of easy fatigability or poor feeding with failure to thrive should alert the anesthesiologist that

this may be a pathologic murmur. A call should be placed to the pediatrician to see if the murmur has been characterized – if not, a pediatric cardiology consult possibly with ECHO may be necessary prior to surgery.

Respiratory Causes

Loss of airway in the pediatric patient has been a common cause of acute deterioration and cardiac arrest. In the POCA data from 1998–2004, the most common causes of respiratory arrest were laryngospasm, airway obstruction, inadequate oxygenation, inadvertent extubation, difficult intubation, and bronchospasm, in decreasing order.[6] Laryngospasm occurred more commonly in children <2 years of age but equally in ASA physical status 1–2 and 3–5 patients. One third of the patients had an upper respiratory tract infection (URI) or copious secretions. The outcomes of arrest following laryngospasm were 80% of patients had no complications, but 20% had negative pressure pulmonary edema requiring intubation. Most laryngospasm (two thirds) occurred during induction and the majority had no IV present at that time requiring IM succinylcholine. One third occurred during emergence or transport. An IV can be very helpful in managing these patients plus intubating as soon as possible if laryngospasm occurs can avoid negative outcomes.

In the patient with a difficult airway, mask ventilation or intubation may be impossible. It is important to maintain spontaneous ventilation with an inhalational agent without the use of muscle relaxants in these patients. A variety of airway equipment is necessary to deal with these situations. This may include various size masks, airways, LMAs, Bullard laryngoscope and pediatric fiberoptic bronchoscopes. Also obstructed tubes, esophageal intubation, or dislodged tubes may precede an arrest. In small children, sounds of air passage may be transmitted from the esophagus and are misinterpreted as being from the airway. Obstruction or kinking of the tube may cause progressive hypoxemia or hypercarbia – making resuscitation more difficult.

Intravascular Volume and Hyperkalemia

Intravascular fluid loss and current volume status are often underestimated in the pediatric patient especially in newborns. Lack of good vascular access can compound these problems. Assessment of intravascular volume depends more on clinical signs than invasive measures that are used in the adult. By the time the pediatric patient becomes hypotensive they are severely behind in fluid and can be close to an arrest situation.

Failure to secure adequate venous access and to keep up with the intraoperative blood loss make these causes of arrest anesthesia related.

Some arrests occur also from not only hypovolemia or hemorrhage, but also from massive transfusion resulting in hyperkalemia. Hyperkalemia from massive transfusion is also potentially preventable by awareness of the problem and using a few steps to reduce the amount of potassium in the transfused blood. As blood ages potassium leaks from the intracellar space into the plasma. This leakage is accelerated in irradiated blood. The anticoagulant used also influences how the blood ages. Packed cells, because of the reduced amounts of plasma have a lower potassium load than whole blood. To decrease the risk of hyperkalemic cardiac arrest the following recommendations will reduce the amount of potassium administered.

1. Use the freshest packed red blood cells available and avoid using whole blood.
2. Don't irradiate the blood except when absolutely necessary (e.g., a premature baby or immunocompromised child). When radiation is required, the time between irradiation and blood administration should be minimized.
3. In high risk situations (e.g., newborn or infant requiring >1 blood volume or with irradiated blood) measure the potassium in the blood to be transfused. If the potassium level is high, consider washing the cells in the cell saver and resuspending the cells in plasma prior to administration.[6]

Inhalational Agents

Anesthetic agent overdose in the face of decreased intravascular volume, is one of the most common causes of sudden hypotension, especially in infants. Bradycardia (<100 beats per minute) is an ominous sign. In a study of causes of bradycardia in infants <1 year of age, 1/3 was due to inhalational agent, 1/3 due to hypoxemia and 1/3 due to patient disease or surgical factors.[11] Inhalational agent overdose responded to a discontinuation of the inhalational agent and atropine in most cases but some needed epinephrine and chest compression. Continuous auscultation of heart sounds is a clinically useful tool for the hemodynamic monitoring of anesthetized infants and children. In a recent study during induction of anesthesia with halothane a dramatic dose dependent decrease in amplitude of S_1 and S_2 heart sounds occurred in all 19 patients ages 6 months–12 years. Monitoring was accomplished by a precordial stethoscope. These changes were clearly audible, occurred rapidly and were followed by corresponding decreases in heart rate and blood pressure.[12] Thus heart sound changes may be an early warning sign of decreased cardiac function and impending disaster. Although sevoflurane has many advantages as to its safety profile it is not the "ideal" inhalational anesthetic agent with there still being concerns about airway fires, emergence delirium, Compound A, and electrical or clinical seizures.

Succinylcholin-Induced Arrest

In infants who have not been given atropine, especially in the presence of hypoxemia, the potential for bradycardia is significant with succinylcholine. Administration of succinylcholine to a patient with unrecognized myopathy can result in massive potassium release and sudden arrest. This is not malignant hyperthermia (MH) which has a slower onset. Also rhabdomyolysis is likely to have bradycardia or arrest as its presenting sign in contrast to tachycardia, tachypnea, arrhythmias, hypertension, and hyperthermia that are common with MH.

Intravascular Local Anesthetic Injection

In the POCA Registry data, intravascular injection of local anesthetic during caudal anesthesia occurred despite negative aspiration and lack of response to a test dose. Incremental rather than bolus injection has been advised for earlier detection of an intravascular injection.[13] Also use of agents with less myocardial toxicity such as ropivacaine may be safer.

Central Venous Catheter Complications

Placement of central venous catheters was the most common equipment-related cause for arrest in the POCA data.[6] Complications included injuries related to needle guidewire or catheter insertion (i.e., pneumothorax, hemothorax, and hemopericadium). Central catheters provide useful information however, maybe inserted more safely with techniques such as ultrasound guidance.[14,15]

INVESTIGATION AND MANAGEMENT OF INTRAOPERATIVE CARDIAC ARREST

1. Pulse oximetry is an early warning sign of developing hypoxemia or decreased perfusion and precedes clinical signs in anesthetized children.[16] If your pulse oximeter stops working and your noninvasive BP monitor keeps reading something is wrong. Don't ignore the monitors.
2. An absent or poor capnograph tracing is indicative of loss of cardiac output or impaired ventilation. It may be the earliest warning of events with the greatest likelihood for significant morbidity, even prior to the onset of desaturation.[17]
3. A stethoscope monitor is invaluable. Changes in intensity of heart sounds may alert you to problems before bradycardia and hypotension become apparent.
4. The airway must be rechecked when the cause of sudden deterioration is unclear. If the patient is not intubated, intubate immediately – if this is not possible (due to a difficult airway) use an LMA or bag and mask ventilation. Children in out of hospital arrests whose airway management was randomized to receive bag and mask ventilation until they reached the hospital had outcomes that were statistically identical to those that were intubated in the field.[18] Look for common problems first - airway, volume status, inhalational agent overdose, etc. Discontinue the anesthetic agents and administer 100% O_2.
5. Start CPR early – to be effective in maintaining adequate circulation a peripheral pulse should be discernible.
6. Vascular access that is reliable can make the difference as to the success of the resuscitation. A free flowing peripheral IV line may be all that is necessary since studies have shown that onset time and peak levels of resuscitation drugs (epinephrine, calcium, sodium bicarbonate, glucose) are similar whether given centrally or peripherally.[19] It is important that peripheral lines are flushed well with 5–10 mL of saline to ensure entry of the resuscitative drugs into the central circulation. If no IV access is present at the time of the arrest, the safest and easiest site to cannulate is the femoral vein, whose measured pressures accurately reflect central venous pressure. If no other access can be obtained, a styleted intraosseous needle can be inserted into the anterior tibia, distal femur, medial malleolus or anterior iliac spine. Any resuscitation drug that can be given IV can be given into the intraosseous space with similar onset times.[19] Drugs that can be administered via the trachea are described by the pneumonic LEAN: lidocaine, epinephrine, atropine, and naloxone. Onset and peak levels of epinephrine administered by this route is delayed as compared to the IV route.[20,21]
7. Epinephrine is the single most useful drug – don't waste time with repeated atropine doses. Although bradycardia is the most frequent rhythm preceding cardiac arrest in children, atropine alone is frequently not sufficient to produce return of circulation. Atropine is the drug of choice only for vagally mediated bradycardia, 0.02 mg/kg IV with a minimum dose of 0.1 mg. After adequate ventilation and oxygenation have been ensured, epinephrine is the drug of choice. The dose recommended by the American Heart Association is 10 μg/kg administered IV every 3–5 minutes or 100 μg/kg intratracheally diluted to 5 mL and followed by five manual ventilations.[20] High-dose epinephrine (100–200 μg/kg) may cause post arrest myocardial dysfunction and necrosis but may be useful if the diastolic pressure is $<$20 mm Hg. Vasopressin (0.4 μg/kg) after two doses of IV epinephrine 10 μg/kg may be effective as a "rescue" medication in prolonged hospital resuscitation.[22]
8. For initial fluid resuscitation current recommendations are to avoid glucose-containing solutions in children unless hypoglycemia is suspected or confirmed. Animal studies have reported that when hyperglycemia is produced prior to a cerebral ischemic event neurologic outcome is worse.[23,24]

This may be because increased lactic acid production in the brain aggravates neurologic injury.

9. Obtain a blood gas and electrolytes early – this can be helpful in determining the cause of the arrest.
10. Routine calcium does not improve outcomes but is indicated for hyperkalemia, hypermagnesiumia, calcium channel blocker excess and documented hypocalcemia. It is not indicated for electromechanical dissociation or asystole.[25,26]
11. Magnesium should be used for hypomagnesemia and Torsades de pointes (polymorphic ventricular tachycardia) at a dose of 25–50 mg/kg with a maximum dose of 2 g.
12. Routine administration of sodium bicarbonate doesn't improve outcomes and should be given only for severe metabolic acidosis, hyperkalemia and hypermagnesemia at a dose of 1 mEq/kg.
13. Obtain a chest radiograph to help rule in or out the cause of the arrest. Tension pneumothorax should be on your differential diagnosis list.
14. Have ready access to a defibrillator. Be sure it is working properly and that pediatric paddles are available. Defibrillation with 2–4 joules/kg is the mainstay of therapy for pulseless ventricular fibrillation (VF) and ventricular tachycardia (VT).
15. Amiodarone can be used for "shock resistant" VF and VT. Amiodarone is a competitive inhibitor of both α and β adrenergic receptors[27] causing both vasodilatation and AV node suppression and is an alternative to lidocaine use an antiarrhythmic agent. The recommended loading dose is 5 mg/kg over several minutes to 1 hour with repeated doses up to 15 mg/kg.

STRATEGIES TO PREVENT CARDIAC ARREST IN THE PEDIATRIC PATIENT

1. Newer inhalational agents and improved monitoring may have already made a difference
2. Use of local anesthetics such as ropivacaine with less potential for toxicity
3. Regional techniques that include aspiration for blood, test dose and incremental not bolus injection
4. Limiting succinylcholine use to rapid securing of the airway and treatment of laryngospasm
5. Adequate IV lines and keeping up with intraoperative blood loss
6. Prevention of hyperkalemia with limited succinylcholine use and during transfusions (beware of old irradiated blood)
7. Early treatment of laryngospasm with the understanding that having an IV in place can be helpful
8. Safer techniques for CVP placement – such as use of 2D US/Doppler
9. Put high-risk children in experienced hands

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Modifying Risk in the ASC: Is There Really Any Risk to Anything We Do There?

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You are the Medical Director of a busy ASC in which an ophthalmologist is performing a line-up of 15 cataracts today. At 11AM, the admitting RN tells you that a 75-year-old man is scheduled for the next cataract extraction and IOL under topical anesthesia with an RN in attendance for any needed sedation. In the preoperative interview, the patient revealed that he plays tennis 3 times per week and passed his annual physical with "flying colors" 6 months ago. Yesterday during his regular weekly tennis match he experienced chest pain with nausea and shortness of breath that caused him to stop playing. This resolved within in a few minutes of rest and has not recurred. He "looks and feels great" and is ready to go. She wants to know if they should proceed with the scheduled procedure. You provide her the correct answer based on your exact knowledge of the calculated risk of proceeding.

What did you tell her?

(Anesth Analg 2008;106:●●●–●●●)

Research characterizing the risk of perioperative mortality and morbidity has focused primarily upon high-risk surgery and patients with severe comorbidities, as well as global patient populations, but rarely upon ambulatory, "low-risk" surgical populations. Ironically, determining the risks of treatment in the latter group may actually be more needed. This is because humans tend to magnify risks when they are rare and discount or stoically accept them when well known,[1] meaning that exact delineation of risks in ambulatory patients may be more important to the informed consent process than it is for patients who already perceive their position as "high risk."[2] For example, you would not be delivering the news for the first time to a patient undergoing CABG if you broach the subject that they could die in the next 30 days (as high as a 6.6% chance, if over the age of 65[2]) or sustain a significant cardiac or cerebrovascular impairment (6 to 12%, depending upon the coexistence of peripheral vascular disease[3]). You almost assuredly would be the first to openly discuss intraoperative death with the parents of a patient about to undergo a myringotomy, but you would undoubtedly find that they have thought about it extensively and that they are worried about it as much or more so than are the family members of the CABG patient.[2]

It is sometimes useful to discuss *relative* risk with patients, when the risk of catastrophic events are lower for the perioperative period than some other very accepted activity ("instead of just staying home, you immediately doubled your chances of dying by getting into the car today; while you are with us, you

[1]For instance, we admonish loved ones to "fly safe" as they head off to the airport because we are briefly considering the rare but catastrophic chance of an airplane crash. However, we completely ignore the much more likely risk of death attendant to the taxi ride to the terminal.

[2]This discussion engenders the concept of 'acceptable' risk, which is dependent upon individual perception of risk vs. reward and informed choice. Most patients believe (correctly or not) the value of CABG to be to diminish the risk of death over the long-term and consequently will accept a higher risk of short-term failure in order to achieve that long-term safety. For them the risk is both *tolerable* (makes logical sense in view of the procedure's invasiveness and their own health) and is *acceptable* (they want the potential outcome to the extent that – for them - the risk is overbalanced by the benefit potential). On the other hand, parents of a child undergoing myringotomy understand its value "only" to be a decrease in ear infections and potentially improved learning and speech over the course of their child's life, and so would probably not consider a 1 in 20 risk of death as *acceptable* to achieve those potential goals (outcomes about which they have not received any guarantee), whereas if we could imagine that a situation existed such that a child was so critically ill that this 5% chance was an accurate risk assessment, an independent observer might consider that level of risk to be *tolerable*. In this way, risk of death is "acceptable" to the cardiac patient, meaning that this risk is understood to be necessarily a part of achieving the desired risks; it is also "tolerable" because there is no perceived alternative to its incursion. On the other hand, we have achieved such a safety record in the outpatient surgery setting (*tolerable* risk levels have dropped) that no risk is considered *acceptable*. In fact, in both the mind of the caregiver and the patient, the categorical separation of 'minor' negative outcomes (nausea) from "major" negative outcomes (stroke) is based upon the level of tolerance for the latter ("zero") vs. the former ("some"). Industrial engineering is more specific in regard to 'acceptable' and 'tolerable' risks, as well as the gray area of ALARP ("as low as reasonably practicable") risk, which presupposes that the operator has done everything possible to reduce risk by first assessing risk factors and then implementing means to decrease the impact or occurrence of such factors – efforts limited by practical constraints of cost. For further discussion, see Aven T. On the Ethical Justification for the Use of Risk Acceptance Criteria. Risk Anal, 2007;27:303–312.

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have dropped those chances back to being 22 times safer than they were if you stayed at home."[4]). An extremely anxious patient is usually surprised and pleased to hear that the specific risks about which he or she is concerned are improbable. Thus, the ideal discussion with someone who is anxious would include the question, "What specifically are you concerned about occurring today?" Often it will not be death, but the famous "fate worse than death," such as not waking up from anesthesia or paralysis after spinal,[5] and your response would include the relative probabilities of those particular risks while at the ASC versus in everyday life. The problem is that we are not in a position to give an accurate assessment of many of those risks, due to the deficits in research mentioned above. That knowledge deficit becomes more clearly significant when you consider the following questions:

What if one of your patients does want to know the specific level of risk he or she is incurring today in your ASC for nausea, vomiting, malignant hyperthermia, seizures, intraoperative fire, aspiration, nightmares, insomnia, pain requiring admission to control, unrecognized cognitive dysfunction due to an intraoperative event, hypoxemia with resultant severe mental deficiency, medication error resulting in permanent harm, allergic reaction, inability to intubate? How many of these answers do we know? How closely do you monitor your own outcomes?

When is the last time an anesthesia provider said this to a patient, "Well, I want to assure you that it is unlikely you will die here today, but it is possible that the way I care for you here will increase the chances that you will die within the coming month, or might make it more likely that your cancer that we are taking out today will come back. In fact, I will be increasing the chances that one of these horrible things happen to you by_____%"?

This review will be unsatisfactory: we don't know enough about the risks of what we do to patients, or the risks of what our patients do to themselves. In addition to the need to study large populations to determine "real" risk, a significant issue that leads to the imprecision of our understanding of risk is our lack of clear definitions regarding what we all mean when we use terms referring to outcomes. This was well explicated by the recently published study regarding "intraoperative hypotension" and the accompanying editorial.[6,7] If we cannot agree on when a death had to occur before it can be partially or fully attributed to anesthesia/surgery, or what we exactly mean by "nausea," then our ability to study the incidence of these events is essentially ablated.

The aim of this lecture is to explicate as much as possible the relative risk of outpatient anesthesia and surgery, what factors increase that risk, how such risk can be ameliorated, and finally how to discuss the issue of risk with patients in an intelligent, informed and reassuring manner.

What Are the Important Aspects of Risk to Include in the Preoperative Discussion?

Significantly for preoperative discussions of risk, perceived risk is increased by lack of personal control over outcome and uncertainty of outcome.[8] Ideally, discussions of anesthesia risk would acknowledge the "naturalness" of concern about this loss of control and would serve to reiterate the relative certainty of anesthetic outcome.

Ethical principles and informed consent law both require the anesthesia provider to give a reasonably accurate picture of risk associated with the options available to the patient.[9] However, each of us has prejudices in this arena. We all tend to be guided by what has been called the "availability heuristic." that is, we choose to warn our patients about specific risks and to make therapeutic decisions based on what experience is available to us in our most recent memory.[10] For instance, if a practitioner has had recent experiences of prolonged recovery from spinal anesthesia, he or she won't offer it. Such prejudice can lead to inadvertent misrepresentation of the risk versus benefit choices provided to a patient and is best guarded against by providing the data from the literature and your own outcomes to help both the patient and anesthesia team determine the safest approach.

What Is the Value to Patients of the Risk Discussion?

Anesthesia consent discussions held immediately prior to the surgical event may be limited as a legal event, because patients have already made their decision to proceed with surgery and note overwhelmingly (94%) that the discussion of anesthesia risks has no bearing on that decision to proceed with surgery and anesthesia.[11] Nonetheless, many patients still value the risk discussion as a means of helping them to understand the likelihood of bad things occurring particularly of concern to them (nausea, death). Humans thrive on preparation and crave foreknowledge to avoid the exceedingly negative emotional consequence of unforeseen danger.

Patients worry about the quality of the incipient anesthesia (pain), vomiting, the unknown, and whether or not the surgery will be successful.[12,13] Notably, over 1 in. 10 are concerned that they will die in surgery and fully 20% are concerned about brain damage and coma as a result of anesthesia.[14] These are risks that we should be able to successfully portray as negligible for outpatients. Patients state that specific pre-operative explanations are reassuring, particularly if they emphasize the relative safety of the events that are about to occur.[15]

Indeed, informed consent rarely plays a role in malpractice litigation, cited in only 1% of cases,[16] so the discussion should focus less on the legal transaction and more on a review of the patient's concerns and the (low) probability of those fears becoming reality.

What Exactly Are the Risks of What We Do in the ASC?

Perioperative death. Perioperative death tends to occur in older and chronically ill patients undergoing emergency major surgery.[17] Although rare in elective outpatient surgery,[18] the risk of perioperative death is increased by advancing age, reaching as high as 50 per 100,000 patients in the outpatient hospital setting within 7 days of surgery in the Medicare population.[19]

Death due to anesthesia. Has been quoted as approximately 1 in. 250,000, with comparative probability of mortality due to automobile accidents at 41 per 250,000; accidental injury in the home at 22 in. 250,000 and 9 in. 250,000 from injuries at work.[20] More recently, one study of anesthesia-related deaths in a University hospital suggested the incidence was as high as 1.4 in. 10,000 patients and that 60% of those deaths were due to inadequate performance by the anesthesia provider(s), primarily inadequate fluid management and attention to oxygenation.[21]

Cardiac arrest. In all anesthetics, the risk for perioperative cardiac arrest appears to be 34.6: 10,000 with increased risk found in neonates, children under age one, elderly males, as well as ASA status 3 or higher; two thirds progress to death.[22] In children, death occurs 28% of the time after perioperative cardiac arrest and is associated with higher ASA status and emergency surgery.[23]

MI. After non-cardiac (but not ambulatory) surgery, the risk is between 4.8 and 9.0%.[24] The risk is highest at the time of emergence from general anesthesia and in the presence of tachycardia.[25] An assessed ASA status of III increases this and all perioperative morbidity risk by over two-fold.[26]

Stroke. After non-cardiac (but not ambulatory) surgery, it is between 1 and 4%.[27] Stroke occurs between 0.8 and 2.9% of general surgery patients, with the normal population incurring CVA at 0.1–0.2% annual incidence.[28]

Unexpected overnight stay required. Up to 1.5% of outpatients are admitted unexpectedly after surgery, most commonly for pain management.[29,30,31] That incidence is higher (21 admissions per 1,000 procedures within 7 days of surgery) in the Medicare population.[32,33]

ENT surgery is associated with a high rate, as much as 6.7 to 8.8% in some series, with septoplasty a significant risk.[34,35] ASA III status doubled the risk of admission in that series. Transurethral resection of bladder tumor carries a higher risk of readmission (4.9%).[36] Overnight admission incidence may be increased by obesity in children, increasing the rate by 10 times, from <0.2% in normal children to as high as 2% among the obese.[37,38]

Awareness under anesthesia. Although still requiring study to solve significant questions regarding the role of "anesthetic depth" measurement exact definitions of awareness, and elimination of bias by repeated questioning, the incidence overall seems to be very low (0.36%) and primarily associated with higher risk patients and surgery, less likely to be seen in the ambulatory setting.[39] However, risk factors for awareness potentially attendant to elective "minor" surgery may include the use of total IV anesthesia (TIVA) and concomitant neuromuscular paralysis, two very common combined techniques in ambulatory surgery.[40] Perhaps the safest approach would be to use techniques that include the elimination of neuromuscular paralysis when it is not required for the operative procedure (it is a relatively rare indication in ambulatory surgery) and the addition of inhaled anesthetics when such paralysis is used.

Nausea/vomiting. One third of surgery patients will have PONV if not pretreated, and three pretreatments (droperidol, dexamethasone, ondansetron) all effect an equivalent decrease of 26%, although droperidol was not effective in men.[41] Avoidance of nitrous oxide, volatile anesthetics and opioids will further decrease that incidence.[42]

Recurrence of cancer. use of general anesthesia during primary excision is associated with an almost 50% increase in recurrence of melanoma.[43] Use of paravertebral analgesia for breast cancer surgery is associated with a lower risk of recurrence and metastasis.[44]

Respiratory compromise. Highest rate is one report of 18% of patients under 36 months of age undergoing adenotonsillectomy.[45] Children with active or recent URIs have more adverse airway events, including "major" desaturation, laryngospasm and bronchospasm, all of which were also increased in those children who were intubated.[46] The risk in the absence of URI was between 2% and 4% for most events, but rose as high as 15.7% (desaturation <90%) and 25% (sore throat) in patients with ongoing URI and use of an ET tube.

Aspiration pneumonia. Risk data range from approximately 1 in. 2,000 to 1 in. 7100, with almost half of adult patients developing pneumonitis, and 1 in. 8 requiring mechanical ventilation.[47,48] Emergency patients account for a significant percentage of these patients, however, so that ambulatory elective surgery patient risk should be much lower. All (elective and emergency) children are more likely to aspirate (1:1,000), yet less likely to develop pneumonitis.[49,50]

Difficult intubation. Incidence is around 2%–3% in normal patients and as high as 16%–22% in patients with obstructive sleep apnea, with an AHI >40 associated with an incidence of over 67%; BMI is not a risk factor.[51,52] Unfortunately, prediction of difficult intubation or mask fit is poorly accomplished when relying on typical airway evaluation measurements.[53]

Postoperative mental change. In major surgery, postoperative cognitive dysfunction (POCD) ranges in incidence from 26% at 1week to 10% at 3 months after surgery, compared to 3.4 and 2.8% in controls.[54] Age is a significant factor, so although it is probable that this incidence is lower in ambulatory surgery, it is not clear that this is so. Indeed, no difference in the

long-term dysfunction incidence exists between patients receiving general versus regional anesthesia, suggesting that prolonged exposure to general anesthetics is not the most critical factor. Indications are that there is no increase in anxiety or depression as a result of invasive surgery in most patients.[55]

Prolonged duration of procedure. Is associated with older age and greater physical status impairment[56] and is itself a risk factor for increased morbidity and mortality.

Failed spinal. Incidence has been estimated at 4% but varies associated with provider experience.[57]

Spinal headache. Incidence ranges from 4 to 8% and is increased by younger age, multiple attempts and needle type.[58]

Failure of surgery requiring re-operation. Hernia repair failure is more common with use of local anesthesia in comparison to regional or general anesthesia (between which there was no difference).[59]

Postoperative urinary retention. Risk is increased in patients undergoing rectal or inguinal surgery under spinal anesthesia but <2% of patients were unable to void after surgery prior to discharge, and only 10% of those required catheterization after discharge.[60]

Sore throat. Incidence ranges from over 45% in the presence of endotracheal intubation for ambulatory surgery, with higher risk associated with female gender and younger age. LMA and mask only airway management dropped the risk to between 3% and 10%.[61,62]

Dissatisfaction with care. One study portrayed a 1.1% risk that the ambulatory surgery patient will be dissatisfied with anesthesia care and a 2.5% risk that they will be dissatisfied with global care.[63] Much of the dissatisfaction stemmed from poor management of MAC (pain, poor communication, fear).

What Factors Raise or Lower Risk?

Comorbidity. In higher risk surgery, five comorbidities (ischemic heart disease, heart failure, cerebrovascular disease, renal insufficiency, and insulin-dependent diabetes mellitus) predict an increased likelihood of dire cardiac outcomes (MI, pulmonary edema, cardiac arrest, and cardiac death) in patients over 50 years of age undergoing non-cardiac, non-neurologic surgery as inpatients.[64] The Revised Cardiac Risk Index portrays that six factors determine risk of perioperative cardiac morbidity and mortality:[65]

1. High risk surgery (abdominal, thoracic, major vascular)
2. History of ischemic heart disease (MI, angina, use of nitroglycerin, positive stress test, Q waves, previous coronary revascularization)
3. History of CHF
4. History of stroke or TIA
5. Dependence on insulin
6. Pre-op serum creatinine >177 μmol/L

The presence of 1, 2, 3, or more factors corresponds to a risk of a major cardiac event (MI, pulmonary edema, ventricular fibrillation, cardiac death) in the perioperative period at a rate of 0.4%, 0.9%, 7%, and 11%, respectively. These would be ideal data for all anesthesiologists to have committed to memory. What does this mean for patients undergoing elective surgery in the outpatient setting? It has been suggested that a good rule of thumb would be that *those with a score of greater than 2 should be studied using dobutamine stress echocardiography*, with a quoted predictive value of 38% positive and 100% negative.[66] Other factors that appear to increase the risk of death in the outpatient setting include postoperative myocardial ischemia (ischemia lasting more than 30 minutes is associated with a 2.6 times increase in long-term mortality rates, while episodes of greater than 1 hour are associated with almost a fourfold increase in mortality long term).[67] Chronic congestive heart failure increases the time of stay in PACU by 11%.[68]

Risk factors for pulmonary complications. The American College of Physicians (ACP) has created a risk assessment guideline for increased incidence of pulmonary complications after surgery.[69] Patient factors include (type A evidence) advanced age, ASA class of 2 or greater, CHF, poor functional capability, COPD, albumin level below 35g/L, and (type B evidence) weight loss, impaired sensorium, cigarette and alcohol use. While each of these has a discrete impact on risk of complications, the combination of one or more of them may well increase that risk, but we do not have that analysis. As well, the ACP documents that the impact of our interventions is significant and that events that occur even in ASCs have impact on risk, including upper abdominal surgery, prolonged surgery, emergency surgery ("add-ons"), and general anesthesia. All were induced a twofold increase in risk (the odds ratio for general anesthesia was only 1.83).

Smoking. Smoking decreases overall average stay in the PACU and although it has been suggested that cessation <2 months prior to surgery may not be useful,[70,71] some studies show that healing outcomes may be improved by any period of abstinence.[72] Smoking does not appear to consistently increase risk for major perioperative morbidity, but is associated with minor respiratory events in patients with reactive airway disease.[73,74] Smoking is associated with a more rapid discharge from the PACU.[75]

Age greater than 70 years. It is of note that general medical assessment has found that higher mortality among elderly patients is associated with a BMI <26 kg/m^2 and a family history of MI or CVA.[76] Although we pay great attention to obesity, it is likely that we should attend to low weight as well in assessing risk in the elderly. Advanced age is a significant risk factor for inpatient perioperative mortality.[77] Recently, a review of Medicare data showed that age is related to an increased risk in outpatients as well, with a risk of between 0.025% and 0.05% of death after outpatient

surgery in a hospital setting in the first 7 days after surgery.[78]

Age <36 months. The significance of this age demarcation is in regard to tonsillectomy, as the literature has suggested that patients younger than 36 months are at higher risk of complications after tonsillectomy and should be monitored overnight in the hospital.[79] Age <12 months has been associated with a higher risk of cardiac arrest in all surgery (without discrimination to determine if this association is true for outpatient surgery).[80]

Prematurity. Prematurity and an estimated gestational age below 60 weeks increases the likelihood of respiratory complications on site to as high as 37%,[81] but bronchopulmonary dysplasia (BPD) is not independently associated with an increased risk for postoperative pulmonary morbidity.[82]

Obstructive sleep apnea–pediatric. The most common situation to see OSA in children in the ASC is when they present for tonsillectomy and adenoidectomy. Stratification of the severity of OSA in children is still an uncertain diagnostic process for which history is not dependable, but children under 36 months usually undergo adenotonsillectomy due to disordered breathing, instead of chronic recurrent infection.[83] Thus, using young age as a surrogate for diagnosis of OSA, the literature shows that younger children (thus, children with OSA) incur a risk for complications after tonsillectomy at a rate as high as 20%.[84] Thus, professional societies guidelines call for them to be cared for as inpatients.[85,86,87]

Obstructive sleep apnea–adult. This diagnosis increases the likelihood of difficult intubation by up to10-fold,[88,89] but has not always been found to put patients at increased risk for postoperative admission due to complications.[90] However, the data is poor with regard to patient morbidity and mortality beyond 24 hours postoperatively, and much research is still needed to determine which patients can safely be treated at home and with what level of opioid intake.[91] Untreated OSA puts patients at risk for increased perioperative morbidity and mortality that should be decreased by preoperative treatment with CPAP or BIPAP if only for 2 to 6 weeks.[92]

Malignant hyperthermia susceptibility. In a patient with known MH in the family, it has been suggested that there is a <1% risk of developing MH if a trigger-free technique is used.[93] Many authorities feel it is therefore safe to provide a trigger-free anesthetic to all MH susceptible patients and to discharge them after an extended period of observation (four hours).[94,95]

Obesity. In adults, one study showed no increase in perioperative morbidity in obese adult patients undergoing non-cardiac surgery,[96] although no study looked at ambulatory adult patients in this regard.

Obesity in children. Unlike adults, there is an increased incidence of difficult airway management, prolonged stay, nausea and upper airway obstruction in the PACU with obese children.[97]

ASA classification. In patients undergoing a wide range of non-cardiac surgery, there is a direct correlation between advancing ASA physical status classification and the incidence of perioperative morbidity and mortality, as well as long-term post-operative functional impairment.[98,99] Of note, multivariate analysis showed that the importance of moving from ASA I to II entailed a risks odds ratio (ROR) of <1.6 even in the presence of major surgery, but that an ASA III classification had a calculated ROR of 2.25, which *exceeded that for the class of operation*. Thus, it would appear that patients with an ASA Class III are at significant increased risk for perioperative morbidity and mortality - over double that of ASA I patients – irrespective of how "minor" a surgical procedure is planned.

Hypertrophic cardiomyopathy. HCM increases the odds of death by 61% and of MI sevenfold in non-cardiac surgery, including non-major surgery.[100] In fact, this impact was more pronounced in minor than in moderate risk surgery. This is a good argument that these patients deserve at least one night of overnight monitoring after even minor surgery.

Renal disease. Even mild renal dysfunction is an independent risk factor for morbidity and mortality associated with major surgery[101] and as noted above, an elevated creatinine is a risk factor for the occurrence of perioperative cardiac events. However, creatinine is a poor (non-specific) indicator of renal dysfunction and it is estimated that almost 8% of adults have some degree of chronic renal disease, such that we see these patients probably more frequently than we realize.[102] Nonetheless, no studies delineate the precise risks of chronic renal disease specific to the outpatient surgical setting.

Neuromuscular blockade. as noted above, the presence of induced paralysis (NMB) is a risk factor for awareness under anesthesia and is in most cases unnecessary for optimal surgical field conditions. Reversal may be associated with increased risk of PONV, and therefore it is ideal to eliminate the use of NMB when possible.

The surgeon. There is a wide variety in skill visible in action on the other side of the drape. This factor has been documented and appears to be unrelated to years of experience.[103]

What Can We Do to Decrease Risk?

Preoperative cardiac evaluation. See the comments above regarding indications for dobutamine stress echocardiography. A recent small study of asymptomatic diabetic patients with high risk for cardiac disease indicates that the ACC/AHA guidelines may overstate the need to evaluate and treat such patients prior to elective surgery.[104] Nonetheless, cardiac complications after non-cardiac surgery in patients with diabetes or hypertension *quadruple* the risk of death in the

five years after surgery.[105] In the setting of elective outpatient surgery, such an increase in risk mandates a conservative approach to pre-operative evaluation.

Statin therapy. There is promising evidence that use of statins preoperatively in vascular and cardiac surgical populations reduces post-operative morbidity and mortality.[106] However, data is insufficient to support the value of statins in the outpatient surgery setting.[107]

Beta-blockade. Beta-blockade given preoperatively to diminish cardiac risk has become controversial. The most recent ACC/AHA guidelines call for their use in patients who are already receiving them or for those patients having vascular surgery whose risk has been defined by ischemia documented on a stress test. The guidelines cite insufficient data to make a recommendation in the presence of low-risk surgery.[108] It should also be noted that not all β-blockers are equally effective.[109]

Coronary revascularization, balloon angioplasty, or coronary stenting. Although each has intrinsic value, when chosen as a method to improve perioperative morbidity risk, none of these have been shown to clearly be of value in comparison to medical therapy. Additionally, plain metal stents should be in place for at least 6 weeks and anti-platelet therapy complete prior to elective surgery[110] and drug-eluting stents appear to require prolonged platelet therapy (at least 6 months) to decrease risk of thrombosis. Consequently, if interventional coronary revascularization were considered necessary prior to surgery, balloon angioplasty at least two weeks prior to surgery would be the best course.[111]

Chest radiographs. in the absence of undiagnosed symptoms, preoperative chest radiographs are of no apparent value in diminishing risk of negative perioperative outcomes.[112]

Choice of anesthetic. controversy still exists regarding the value of anesthetic choice in diminishing risk of perioperative morbidity and mortality. Use of intraoperative or postoperative epidural analgesia was determined not to be of value in decreasing pulmonary complications after surgery by the American College of Surgeons,[113] yet it is probable that the mixture of lumbar epidurals with thoracic epidurals in many of the studies reviewed by meta-analyses has potentially diluted the positive impact on specific types of morbidity achieved by the use of appropriately targeted blocks in specific types of surgery.[114] General anesthesia is associated with more post-outpatient surgery admissions in elderly patients than is regional, with general anesthesia increasing the odds by over 6 times.[115] One of the more disturbing findings is that of the association of the use of general anesthesia and higher rates of tumor return, as high as 50% in one study.[116]

PONV. can be reduced by use of dexamethasone and ondansetron if the former is given early in the procedure and also can be reduced in women by using droperidol.[117] Avoidance of opioids, nitrous oxide, and volatile anesthetics can reduce risk, but the role of neostigmine is controversial as a risk for PONV.[118,119]

CONCLUSION

What Should Your Informed Consent Discussion Mention in Regard to Perioperative Risk?

No single approach to explaining risk will work for all patients, as humans do not use a rational thought process in assessing risk, with fear playing a significant role for many people in their consideration of risk when planning their own behavior.[120] This has been shown to be true in regard to regional anesthesia, where one study showed that 27% of patients were "very concerned" about paralysis when considering a spinal for knee surgery.[121]

The use of comparative probabilities is a useful approach in view of our inability to precisely characterize probability or risk attendant to our care. In general, humans accept a risk of death of 10^{-6} but not as high 10^{-4} per year.[122] Most data would support the concept that the risk of death associated with outpatient anesthesia and surgery is within this range of acceptable risk.

Yet it must be noted that patient understanding of the most straightforward delineation of risk is widely variable, including the use of numerical figures to describe likelihood.[123] So, in your pre-anesthesia discussion, I think you can correctly tell your outpatients the following (assuming they are not undergoing vascular surgery, have <2 cardiac risk factors, have a functional capacity of greater than 4 Mets and an able caregiver to take them home and stay with them there):

"Statistically, your chance of a catastrophic event occurring to you today or in the next month, like death, a stroke, a coma or paralysis is not increased by having surgery here today."

Further guide the discussion, when you have presented the information that you consider to be important, by adding the question, "What specifically are you concerned about occurring today?"

Finally, it is clear from this discussion of risk and our lack of knowledge that it is important for each ASC and practitioner to track their own outcomes, to be able to quote your own data when the literature cannot help. It is of inestimable value to be able to tell your patient that the nausea rate at your center is under 4% for all patients, rather than "studies have shown that up to a third of patients can have nausea after surgery but we'll try to decrease your risk with the use of medication." Not only will the data reassure the patient that he or she is in adept hands, but also that you care enough about the risk to measure it – that inspires confidence! Simple use of spreadsheets and clerical data input will provide you fodder for improvement in your center as well as a means to

reassure your patients of the high quality of care that you provide there.

What about our tennis player with the new chest pain ready for his cataract surgery? Of course, that patient's entry into your surgery center should be viewed as serendipitous for his outcome and the first step into the process of urgent cardiac evaluation. He should not undergo cataract surgery, but should have his unstable angina evaluated this morning, with definitive therapy guided by the cardiologist's findings.[124] You have no idea what his coronary status is, but his risk of death in he next 30 days, *even if treated*, is potentially as high as 1 in. 10, and as high as 15% in the next year.[125] His lens will have to wait!

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Caudwell Xtreme Everest

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The study of human physiology perturbed by exposure to extreme environments has been proposed as a useful approach for obtaining novel data to improve our understanding of both physiology and pathophysiology. Parallels between physiological patterns of response at altitude and in critically ill patients have been suggested. Genetic associations with beneficial adaptation or outcome are common to both contexts. Caudwell Xtreme Everest, a study of adult human physiological responses to progressive environmental hypoxia, was designed to provide data to improve understanding of responses to hypoxia in critical illness. A smaller parallel study described responses to more moderate altitude in children (Smith's Medical Young Everest Study). The strengths and weaknesses of these studies will be discussed along with a summary of the data collected.

The Caudwell Xtreme Everest (CXE) research project was designed to explore human adaptation to hypobaric hypoxia in order to improve understanding of responses to hypoxemia and cellular hypoxia in critically ill patients.[1] A large cohort of healthy volunteers was studied before and during exposure to progressive environmental hypoxia. The aim of the study is to explore variation between individuals in the pattern of response to hypoxia and to identify factors that contribute to this variation. Specific hypotheses relating to tissue and cellular oxygen handling and genotype-phenotype interactions are being explored. The ultimate goal is the development of new treatments and approaches in the care of the critically ill resulting in improved patient outcomes. The Smiths Medical Young Everest Study (SMYES) is a smaller parallel study of children ascending to more moderate altitude and provides novel data in a neglected study group. This article/lecture will explain the underlying concepts behind this approach to exploring human physiology and outline the form and scope of the CXE and SMYES projects.

EXTREME ENVIRONMENT PHYSIOLOGY

CXE developed from the general premise that human physiological and pathophysiological responses to extreme environments can provide novel data that may lead to improved understanding of clinical problems. The hope is that knowledge obtained in this way might lead to the development of new therapeutic strategies resulting in improved patient outcomes. In the context of human physiology and medicine, an extreme environment may be defined as any environment where humans require either physiological adaptation or technological innovation in order to survive.[2] Simple physiological stress does not define an extreme environment; there must be a risk of illness or death in some, if not all, exposed individuals in order to justify the requirement for adaptation or innovation. Although some would propose that the psychological and sociological characteristics of an environment should be incorporated in this definition, this can result in difficulty in distinguishing the simply unpleasant from the potentially dangerous (where survival may be at stake).

This approach of studying healthy humans in extreme environments is justified if three conditions are met: the data produced should be shown to be valuable; the data is obtained more efficiently using an extreme environmental study or cannot be obtained in any other way; and the risk of the environment is acceptable to the subjects. The last of these conditions is made explicit by written informed consent that clearly includes discussion of any environmental risks of the study. Clinical benefit is most readily apparent when a new finding leads directly to a change in practice (e.g., novel therapeutic agent or management strategy) resulting in improved outcomes for patients. Benefit may also be obtained by observations or empirical findings leading to developments in understanding of pathophysiology that contribute more generally to future clinical developments.

ADAPTATION TO HIGH ALTITUDE AS A MODEL FOR CRITICAL ILLNESS: THE CXE HYPOTHESES

The role of hypoxia in critical illness and the possible relationship between responses to hypoxia at high altitude and critical illness have been explored elsewhere.[3] Cellular hypoxia may be both cause and consequence of a variety of conditions common in critically ill patients. Few if any critically ill patients do not have marked cellular hypoxia in at least one organ system. Hypoxia may trigger inflammatory pathways, and inflammation may in turn lead to localized or more generalized hypoxia. Adaptive responses to hypoxemia at altitude in part reflect patterns of response in critical illness. Oxygen consumption and flux (delivery) is commonly increased in the acute phase of critical illness and following the trauma of major surgery; the response to acute hypoxemia during early exposure to altitude is to increase oxygen flux (elevation of cardiac output and hemoglobin). At this stage, augmenting oxygen delivery by increasing blood flow or oxygen content may improve outcome in critically ill and post-surgical patients. Conversely, in established critical illness the reverse is true: oxygen consumption tends to fall and deliberately increasing oxygen delivery has no benefit or may even cause harm. A similar pattern pertains in well-acclimatized individuals where limitation of oxygen consumption seems to be an important feature of the adaptive process. Furthermore, allelic variants of ubiquitously expressed genes (Angiotensin Converting Enzyme) associated with improved outcomes in several critical illnesses (e.g., ARDS) are also associated with improved performance at extreme altitude.

A paradox at the center of altitude physiology is that variations in performance at altitude are not explained by either sea level performance or resting oxygen delivery at altitude (product of cardiac output and oxygen content). Furthermore, relative differences in physiological variables thought to be responsible for "acclimatization" (e.g., ventilation, cardiac output, and hemoglobin) do not explain differences in observed performance. Changes in tissue or cellular oxygen handling might provide an explanation for this puzzling situation. Possible mechanisms may include alterations in microcirculatory flow leading to impaired cellular oxygen delivery, limitation of oxygen diffusion within the tissues, and variation in relative cellular metabolic efficiency (modification of the relationship between oxygen consumption and work). If cellular metabolic efficiency does change in some subjects, and the underlying mechanisms can be identified, then the implications would be significant. A therapy capable of altering the relative efficiency of cellular oxygen use might allow less aggressive targeting of oxygen delivery in some critically ill patients. This in turn has the potential to reduce the known adverse effects associated with some of the strategies to improve oxygen availability at a cellular level (mechanical ventilation, high-inspired oxygen levels, blood transfusion) and potentially improve patient outcomes.

CXE set out to test the hypotheses that alterations in performance at high altitude might be explained by changes in microcirculation blood flow (and hence local oxygen delivery) or by alterations in cellular "metabolic efficiency," the ratio between work output and oxygen consumed. We also set out to explore the hypothesis that inter-individual variation in observed adaptive changes would be related to variation in the frequencies of alleles of candidate genes. Specific candidate genes will include those implicated in mediating changes in "metabolic efficiency," known hypoxia sensitive genes, and genes known to be unregulated during fetal life. The possibility that physiological pathways identified as beneficial or maladaptive in fetal life, may be associated with similar effects in adults exposed to conditions of profound hypoxia/hypoxemia is particularly intriguing. Recent advances in the understanding and investigation of fetal gene expression may give new life to Sir Joseph Barcroft's oft quoted analogy of "Everest *in utero*".[4]

Clearly the study of healthy individuals exposed to hypoxia at high altitude has limitations as a model for critical illness. However, alternatives may have equivalent or greater limitations and studies in critically ill patients are fraught with difficulty. Patients with critical illness are a heterogeneous population. They have a variety of presenting complaints, preexisting illness, and subsequent patterns of organ failures and are receive a variety of treatments. One consequence of this heterogeneity is that separating out the specific effects of an individual variable can be very difficult: the signal to noise ratio is very low. The limitations of animal models have been highlighted by the repeated failure of antisepsis treatments that have shown no benefit in humans despite promising results from studies in animals. Cellular and molecular studies are an important component of patient, volunteer, and animal studies, but on their own are no substitutes for exploring integrated physiology at a whole organism level. Increasingly, complex computer models have huge potential, but the validity of current models is still uncertain and they rely on iterative process with regular "reality checks" from human data. Studies in hypobaric chambers are a possible alternative to field studies at high altitude but have several disadvantages. Prolonged chambers studies are expensive, not least due to the requirement for continuous medical and technical staffing and capacity is limited (CXE involved more than 11 person years of subject exposure to hypobaric hypoxia). Finally, recruitment of more than 200 healthy volunteers for research during a trek in the Himalaya is feasible; it is doubtful whether the same could be achieved for a 2-week chamber exposure.

THE CAUDWELL XTREME EVEREST STUDY

CXE is the largest human high-altitude experiment ever conducted and builds on work conducted during previous high altitude[5] and chamber studies.[6] The strengths of CXE are the large number of subjects studied and the unique data collected near to the summit of Everest. During the first 6 months of 2007, more than 200 healthy volunteers were studied at sea level in London and at four field laboratories at increasing altitudes up to 5300 meters (Everest Base Camp) in Nepal. Fifteen climbing investigators went through the same tests and then ascended high on the mountain to make novel measurements up to and above 8000 meters. More than 60 investigators were involved in data collection. The strengths of CXE recruited many more subjects and many more subjects and conducted.

The core studies were designed to map out changes in exercise capacity and exercise efficiency during progressive exposure and adaptation to the hypoxic environment. Oxygen consumption was measured using Cardiopulmonary Exercise Testing (breath-by-breath respiratory gas analysis) while pedaling a cycle ergometer. Subjects were exercised to exhaustion to explore exercise capacity (anaerobic threshold and maximum oxygen consumption) while exercise efficiency was investigated using a steady-state protocol. During exhaustive exercise cerebral and muscle tissue oxygenation were monitored using Near-Infrared Spectroscopy. Subjects filled in a daily symptom diary and recorded simple physiological variables (including oxygen saturations) before and after a standardized exercise challenge (CXE Step Test). Additional studies on all subjects included spirometry, and a detailed neurological assessment ranged from simple pupillary responses to a complex neurocognitive battery lasting up to 45 minutes.

Subgroups of the base-camp and climbing investigators were studied in more depth. ECG, echocardiography, transcranial Doppler recording of the middle cerebral artery and real-time imaging of the microcirculation provided valuable data. Invasive techniques including intra-arterial cannulation, muscle biopsy, and gastrointestinal tonometry allowed more precise description of adaptive changes. Arterial access allowed continuous monitoring of cardiac output and blood pressure during exercise as well as serial sampling of biological markers. Muscle biopsies will allow us to explore the transcriptome and proteome in order to explore whether observed variations in allelic frequencies result in changes in gene products. Conversely, the availability of tissue to explore patterns of transcription and expression may allow identification of novel candidate genes to explore the relationship between observed phenotype and allelic variation.

Although complex imaging techniques are impractical in remote environments, several studies involved Magnetic Resonance Imaging (MRI) before and after the altitude exposure. These studies explored both structural predisposition to hypoxia related pathology and, in the climbers, subtle changes associated with prolonged significant hypoxemia. In addition, a small group underwent functional MRI studies and these should contribute substantially to our understanding of the metabolic changes induced by prolonged exposure to hypoxia.

Higher on the mountain, arterial blood gases were obtained at 8400 meters while descending from the summit and a novel semi-closed breathing system was evaluated above 6000 meters.

The SMYES study followed 9 children of 6 years and older as they ascended to nearly 4000 meters in the foothills of Everest. The children were already traveling to the region with their parents who were involved in the CXE study and the opportunity was taken to obtain some simple observational data. Measurements included oxygen saturations, end-tidal CO_2, spirometry, sleep studies, and symptom scoring. These data are among the first available in this group of subjects and provide a stepping stone to future studies as well as demonstrating the feasibility of safely studying children in this environment.

CONCLUSION

The output of these studies so far is a huge amount of novel data. Data entry on the main study database was completed in December 2007, and the dataset is currently being validated and quality controlled. Exercise test analysis and data management will be completed by June 2008. The first of a planned series of primary publications are currently in peer review. The investigators hope that as the data is analyzed and the hypotheses confirmed or refuted, that a new phase of translational clinical studies in critical care and high-risk major surgery will be driven by the novel results.

ACKNOWLEDGMENTS

Caudwell Xtreme Everest (CXE) is a research project coordinated by the Centre for Altitude, Space and Extreme Environment Medicine, University College London, UK. The aim of CXE is to conduct research into hypoxia and human performance at high altitude in order to improve understanding of hypoxia in critical illness. Membership, roles and responsibilities of the CXE Research Group can be found at www.caudwell-xtreme-everest.co.uk/team. The research was funded from a variety of sources, none of which are public. The entrepreneur John Caudwell, whose name the expedition carries, donated £500 000 specifically to support the research. BOC Medical, now part of Linde Gas Therapeutics, generously supported the research early on and continues to do so. Lilly Critical Care, The London Clinic (a private hospital), Smiths Medical, Deltex Medical and The Rolex Foundation have also donated money to support the research and logistics. All monies were given as unrestricted grants. Specific research grants were awarded by the Association of

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Anesthetic Management of the Adult Patient with Congenital Heart Disease

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Because continued improvement in the outcomes of congenital cardiac surgery has created a growing population of adults with repaired or palliated congenital heart disease (CHD), equal numbers of adults and children now have CHD. Almost all children with CHD are operative candidates, and surgery results in approximately 95% survival. Adult CHD patients may present for primary repair of their congenital lesion, final repair after previous palliation, surgical revision because of failure or lack of growth of a bioprosthetic material, conversion of an earlier repair to a more modern one, and noncardiac surgery.

Providing the optimal perioperative management for these patients can be challenging. They have congenital heart defects, such as shunt lesions and single-ventricle physiology, which are most familiar to pediatric specialists. However, these patients may also have coexisting diseases of adulthood, such as coronary artery disease and chronic renal insufficiency, which are best managed by a specialist in adult diseases. For this reason, many regionalized centers that treat adults with CHD have a multidisciplinary team that provides perioperative and follow-up care.

Despite the growing number of operations performed on adults with CHD and the development of an entire subspecialty devoted to the care of these patients, limited data exist concerning their anesthetic, intraoperative, and perioperative course. Most reviews of operations for adults or teenagers with CHD have focused on long-term results.

CARDIAC COMPLICATIONS

Arrhythmias

Adults with CHD have an increased incidence of arrhythmias, which may be classified as intra-atrial re-entrant tachycardia, ventricular tachycardia, heart block, or sinus node dysfunction. Usually, intra-atrial re-entrant tachycardia affects patients who have had extensive atrial dissection and repair, including the Mustard or Senning procedure (see Transposition of the Great Vessels, later) or the Fontan procedure (see Single Ventricle, later). More than 40% of these patients develop intracardiac thrombi, and the sudden death rate is 6% to 10%. The risk for ventricular tachycardia increases with advancing age and poorer hemodynamic status. Antiarrhythmic therapy suppresses symptomatic ventricular arrhythmias but does not prevent sudden death. Bradyarrhythmias may result from surgical injury of the sinus node or atrioventricular conducting tissue or from spontaneous complete heart block. Sinus node injury most commonly occurs during the Mustard, Senning, or Fontan procedures. In contrast, atrioventricular conduction injuries tend to occur during ventricular septal defect (VSD) closure, left ventricular outflow resection, or Tetralogy of Fallot repair. The incidence of complete heart block increases by about 2% per year in patients with ventricular inversion.

Pulmonary Hypertension

Patients with lesions that involve left-to-right shunts are at risk for pulmonary hypertension and pulmonary vascular obstructive disease. Exposure of the pulmonary vasculature to systemic pressure or excessive flow causes a progressive morphologic change in the microvasculature, which initially manifests as medial hypertrophy, and then it progresses to necrotizing arteritis. Pulmonary vascular resistance increases, eventually leading to right-to-left shunting with associated hypoxia and erythrocytosis (Eisenmenger syndrome). This syndrome develops earlier and more commonly among patients with high-flow, high-pressure, systemic-to-pulmonary shunts, as seen in truncus arteriosus. Without surgical repair, Eisenmenger physiology will develop in approximately 50% of patients with a VSD or patent ductus arteriosus (PDA) but in only 10% of those with an atrial septal defect (ASD). If Eisenmenger syndrome is not diagnosed until adulthood, the prognosis is generally poor, the average life expectancy being <6 years from the time of diagnostic catheterization. Cardiac catheterization should be performed in these patients to determine the angiographic appearance of the pulmonary vascular bed and to determine whether pulmonary vascular resistance decreases with 100% oxygen or other pulmonary vasodilators, such as nitric oxide or prostacyclin. In patients with fixed, irreversible pulmonary hypertension, attempted surgical repair of the shunt yields substantially increased morbidity and mortality. Lung transplantation should be considered in patients with good cardiac function, and combined heart-lung transplantation may be suitable for those with deteriorating cardiac function or complex CHD.

tension, the survival rate is 72% at 1 year and 42% at 5 years; the survival rate is similar after a single or double lung transplant.

Ventricular Dysfunction

Congenital heart anomalies place a pressure or volume burden on the heart, causing the myocardium to become hypertrophied or dilated. If the hemodynamic load is relieved by means of surgery or interventional cardiac catheterization, myocardial remodeling occurs, permitting normal or near-normal myocardial performance. However, hemodynamic abnormalities that are corrected later, after age 10 years, commonly produce long-standing ventricular dysfunction. Chronic cyanosis exacerbates the abnormalities of ventricular performance.

Other Systemic Diseases Associated with Congenital Heart Disease

Pulmonary disease

Patients with cyanotic CHD require increased minute ventilation to maintain normocapnia. This requirement is because venous blood, which is rich in carbon dioxide, bypasses the lungs because of an intracardiac right-to-left shunt (i.e., there is an increase in physiologic dead space). Because of this dead space, end-tidal carbon dioxide monitoring will underestimate the amount of arterial carbon dioxide. Although cyanotic patients have normal increases in minute ventilation caused by increased carbon dioxide, they have a blunted ventilatory response to hypoxemia that improves after surgical correction of hypoxemia.

Renal disease

In CHD, chronic cyanosis produces a renal histopathology characterized by hypercellular glomeruli with basement membrane thickening, focal interstitial fibrosis, tubular atrophy, and hyalinization of afferent and efferent arterioles. In one study, more than 13% of surgical patients with cyanotic CHD developed postoperative acute renal failure after undergoing cardiopulmonary bypass.

Hematologic disease

Long-standing cyanotic CHD leads to erythrocytosis and blood hyperviscosity. As the hematocrit and viscosity increase, oxygen delivery eventually decreases because of the diminished cardiac output. Severe polycythemia also leads to coagulation and platelet abnormalities. At the time the hematocrit exceeds 65%, hemorrhagic and thrombotic complications will be reduced if a prophylactic isovolemic phlebotomy is performed before elective surgery.

Neurologic disease

Patients with an intracardiac shunt are at risk for cerebral emboli and brain abscesses. Children with severe polycythemia are vulnerable to cerebral venous and arterial thrombosis. Patients with CHD may have Moreover, adult patients who had cardiac surgery during the early years of extracorporeal circulation may have undergone prolonged deep hypothermic arrest and had air or particulate emboli. Such patients may have residual neurologic deficits or seizures.

Other congenital anomalies

More than 25% of patients with CHD have associated noncardiac anomalies, most commonly orthopedic and genitourinary malformations. Thirteen percent of CHD patients have a chromosomal abnormality, and 5% have a syndrome or heritable disorder. To detect such anomalies, especially malformations of the airway, these patients should undergo a thorough review of their various systems and a focused airway examination.

SPECIFIC CARDIAC LESIONS

Atrial Septal Defect

Because many such patients are asymptomatic, they may present for primary repair in adulthood. Because complications such as tachyarrhythmias and paradoxical emboli increase in frequency with aging, however, repair is ideally performed in childhood. Surgical closure after 5 years of age is associated with incomplete resolution of right ventricular hypertrophy, and survival is worse when ASD is closed after 24 years of age.

Ventricular Septal Defect

Most small-to-moderate VSDs will close in the first decade of life. Children with larger VSDs will have congestive heart failure and may develop irreversible pulmonary hypertension if closure is delayed. Delayed surgical closure may also place the child at risk for ventricular dysfunction years after surgical repair. Adults are at increased risk for aortic insufficiency resulting from valve prolapse into the defect.

Patent Ductus Arteriosus

Persistence of a PDA leads to a high-pressure shunt from the aorta to the pulmonary artery. This left-to-right shunt places a volume burden on the heart and, if the PDA is large, will lead to end-stage pulmonary hypertension. In adulthood, the ductus may become calcified or undergo aneurysmal dilation, and cardiopulmonary bypass or deep hypothermic circulatory arrest may be necessary to control blood flow to the ductus during repair.

Coarctation of the Aorta

In coarctation of the aorta, long-term left ventricular obstruction leads to ventricular hypertrophy, premature coronary atherosclerotic disease, and a poor long-term outcome after repair in adulthood. In patients undergoing repair after the 40th year of age, the 15-year survival rate is 50%, and half of the patients have persistent hypertension. Patients operated on

during childhood may develop an aneurysm at the repair site or have recoarctation requiring repeat surgery; 5 years after primary repair, the incidence of recoarctation approaches 20%.

Valvular Anomalies

Congenital abnormalities of the semilunar or atrioventricular valves may cause stenosis or regurgitation, and the anesthetic considerations are similar to those for acquired valvular disease.

Transposition of the Great Vessels

Without surgical intervention, patients with transposition of the great vessels die in infancy. Before 1980, the most common surgical treatment for this defect was the atrial switch (Mustard or Senning) procedure, in which systemic blood returning to the right atrium is directed to the mitral valve, and pulmonary venous blood is directed to the tricuspid valve. With this procedure, the right ventricle remains the systemic pump. Postoperatively, however, the incidence of atrial arrhythmias and sinus node dysfunction increases with time because of extensive atrial suturing and possible injury to the sinus node artery during surgery. In addition, tricuspid insufficiency and right ventricular failure develop in some patients, who are candidates for valve replacement or surgical conversion to the arterial switch procedure. Because the left ventricle is the pulmonary pump, patients must undergo progressive arterial banding to "train" the left ventricle to become the systemic pump or must use a left ventricular assist device as a bridge to recovery. In the 1980s, the arterial switch procedure became the operation of choice for most patients. Its long-term outcome is believed to be better, but concern remains about growth of the coronary anastomotic sites and development of aortic valve insufficiency.

Congenitally Corrected Transposition of the Great Vessels (L-Transposition, Ventricular Inversion)

In this congenital malformation, the physiologic left ventricle is the pulmonary ventricle, and the physiologic right ventricle is the systemic ventricle. This anomaly is associated with a VSD in 80% of patients. In the absence of associated lesions, the malformation may be unrecognized in childhood. With increasing age, the systemic (right) ventricle tends to fail, leading to tricuspid valve insufficiency. Also, arrhythmias develop in about one third of patients, heart block being the most common form. A newer surgical correction, the double switch procedure, may be performed in adolescence or early adulthood. In this procedure, an atrial switch (the Senning baffle procedure) and an arterial switch are performed, making the anatomic left ventricle the systemic pump. Before this procedure is undertaken, the patient must undergo pulmonary artery banding to "train" the left ventricle.

Ebstein's Anomaly

In Ebstein's anomaly, the attachment of the tricuspid valve is displaced downward, creating a malformed (small) right ventricle, with an atrialized portion of the right ventricle between the tricuspid valve annulus and the attachments of that valve's posterior and septal leaflets. Patients may present in infancy with cyanosis or later in life with congestive heart failure or cyanosis; some adults are asymptomatic and have a normal life expectancy. Almost half of the patients have arrhythmias, most commonly supraventricular ones, and many patients have the accessory pathway of Wolf-Parkinson–White. In adults with this disease, the most common surgical procedure is tricuspid repair or replacement. Atrioventricular block is common after tricuspid replacement.

Tetralogy of Fallot

Most patients with Tetralogy of Fallot undergo surgical repair in childhood, although primary repair in adults can also yield a good outcome. Currently, the VSD associated with Tetralogy of Fallot is closed through a right atrial incision; however, adults who have undergone repair may have had a right ventriculotomy for VSD closure. These patients commonly develop ventricular arrhythmias many years after surgical repair and are also at risk for sudden death; however, ventricular arrhythmias may not be the major cause of sudden death. The most common reasons for reoperation in adults are related to the right ventricular outflow tract—pulmonary insufficiency and right ventricular-to-pulmonary artery conduit failure.

Atrioventricular Canal

Atrioventricular canal results from incomplete closure of the endocardial cushions and is associated with a primum ASD, a VSD, and a common atrioventricular valve, usually occurring in patients with trisomy 21. Surgical correction involves closure of the ASD and VSD, division of the atrioventricular valve, and closure of a cleft in the anterior leaflet of the mitral valve. Repair is usually performed in infancy because of the risk for end-stage pulmonary vascular disease. Postoperatively, residual or progressive mitral valve regurgitation is common, with 10% to 30% of patients requiring repeat surgery.

Truncus Arteriosus

In truncus arteriosus, a common semilunar (truncal) valve gives rise to the systemic, pulmonary, and coronary circulations, and a VSD is present below the truncal valve. Surgical repair is usually performed in infancy and typically involves VSD closure, routing the left ventricular blood through the truncal valve, and inserting a right ventricle-to-pulmonary artery conduit to provide pulmonary blood flow. Almost all patients with this type of repair will later need replacement of the pulmonary conduit. In addition,

some patients develop truncal (neo-aortic) valve insufficiency requiring valve repair or replacement.

Single Ventricle

A wide variety of anatomic abnormalities will produce single-ventricle physiology. Most of these patients have atresia of an atrioventricular or a semilunar valve, with complete mixing of systemic venous and pulmonary venous blood. Ventricular ejection into the pulmonary or systemic circulation is based largely on the vascular resistance of these circuits. Most patients require surgical palliation in infancy with either a shunt that provides pulmonary blood flow from the systemic circulation or a pulmonary artery band that limits flow into the pulmonary circuit. These patients will undergo staged repair of their heart disease, eventually culminating in the Fontan procedure. This operation routes systemic venous blood directly to the pulmonary circulation, and central venous pressure becomes the driving force for pulmonary blood flow. With this physiology, negative intrathoracic pressure generated by spontaneous ventilation promotes pulmonary blood flow. Conversion from spontaneous ventilation to positive-pressure ventilation increases the intrathoracic pressure, thereby decreasing pulmonary blood flow, which reduces the ventricular preload and may significantly decrease the cardiac output. The Fontan procedure was originally performed via an atriopulmonary connection. With this anatomy, the right atrium frequently becomes massively dilated, leading to atrial dysrhythmias. Atrial contraction also creates turbulence in the blood stream, reducing effective forward flow. Failing Fontan repairs have been successfully converted to an extracardiac, or lateral-tunnel, Fontan repair. Consequently, systemic blood flows to the lungs directly from the superior vena cava and by way of a large venous conduit or intracardiac tunnel that connects the inferior vena cava and pulmonary arteries, minimizing arrhythmias and improving function.

ANESTHETIC MANAGEMENT

On the basis of the data mentioned earlier and our experience, the following management strategy for adult patients undergoing surgery for CHD is recommended:

1. Preoperative Preparations

a. Patient data should be presented to a multidisciplinary group of cardiologists, surgeons, and anesthesiologists. Data analysis should include the results of laboratory testing, cardiac catheterization, echocardiography, Holter monitoring, chest radiography, and magnetic resonance imaging. The multidisciplinary group should arrive at a consensus about surgical options, which may include cardiac transplantation, and about the timing of surgery.
b. The patient's cardiac rhythm should be assessed, with particular emphasis on the functioning of pacemakers (if present) and on the underlying cardiac rhythm in case of pacemaker failure.
c. An anesthetic plan should be developed in accordance with the patient's unique pathophysiology and anticipated response to anesthetic interventions. This is particularly important for patients with single ventricle and poor ventricular function, who may not tolerate myocardial depressants, positive-pressure ventilation, or loss of sinus rhythm.

2. General Operating Room Care

a. Large-bore intravenous access should be established, and provisions should be made for the rapid infusion of volume. A pressurized rapid-infusion system, capable of delivering at least 500 mL/min of warmed fluid or blood, is recommended. If massive bleeding occurs, rapid infusion can be established with the cardiopulmonary bypass machine: tubing from the venous reservoir is passed through a roller-pump head and connected to a large-bore venous access device. Heparin is administered, and large volumes can be transfused while preparing to institute bypass rapidly via the femoral route.
b. Multifunction external pacing, defibrillating, and cardioversion pads should be applied, and antiarrhythmic drugs should be immediately available. In pacemaker-dependent patients who have very slow or nonexistent underlying ventricular escape rhythms, preoperative insertion of a transvenous pacemaker should be considered.
c. In a preoperative discussion, the surgeon, anesthesiologist, and perfusionist should plan for emergency femoral bypass if necessary.
d. Preparations should be made to treat postoperative hemorrhage. Tranexamic acid, ε-aminocaproic acid, and aprotinin can reduce bleeding in these patients. Adequate blood products, including platelets, fresh frozen plasma, and cryoprecitipate, should be available. Cell salvage, with reinfusion of washed autologous red blood cells, is appropriate. During cardiopulmonary bypass, thromboelastography with heparinase and Celite® (International Technidyne Corporation, Edison, NJ) added to neutralize heparin and speed results may be useful to predict the need for blood products after cardiopulmonary bypass, particularly in patients with a baseline coagulopathy related to cyanosis.
e. Transesophageal echocardiography is indicated for congenital heart operations in infants and children and is equally applicable to congenital heart operations in adults.
f. Neurologic monitoring with transcranial Doppler ultrasonography (to assist in detecting and

limiting cerebral emboli), bispectral index electroencephalography and near-infrared spectroscopy may be helpful in minimizing neurologic complications.

SUMMARY

As the number of CHD repairs in adults continues to increase, these operations will be performed in a wider variety of institutions and systems. Unfortunately, not all of these centers will have an optimal environment for correcting CHD in adults. This type of surgery is best accomplished in a facility specifically designed for treating adults with CHD. Optimal care of these patients is provided by cardiologists who are trained and experienced in pediatric and adult cardiology, by surgeons who are trained and experienced in treating CHD, and by anesthesiologists who are experienced in caring for adults with CHD. Whatever the setting, cardiac anesthesiologists involved in these cases must be thoroughly aware of the anesthetic implications for the unique pathophysiology of each patient, and they must not rely on their "usual" expectations of either true pediatric CHD or acquired adult heart disease.

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Anesthetic Concerns for the Patient with Liver Disease

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Advanced hepatic disease should really be considered a systemic disease process, affecting multiple organ systems. Like kidney failure, it reflects a fundamental defect in protein metabolism, i.e., nitrogen elimination after deamination of amino acids. In renal failure, ammonia is converted to urea, which accumulates as BUN. In liver failure, the arginine cycle fails to convert ammonia to urea, so that ammonia accumulates and blood urea nitrogen (BUN) remains very low. In fact, hyperammonemia is a marker for other circulating byproducts of protein metabolism that cause defective ion transport across cell membranes, resulting in intracellular sodium and water accumulation. Every organ system is affected.

Patients with advanced hepatic disease present a challenge to anesthesiologists because liver failure implies abnormal handling of anesthetic agents, as well as multiorgan system dysfunction, general debility and specific problems associated with replacement therapy and transplantation. Moreover, when hepatic insufficiency is severe, anesthesia and surgery may themselves precipitate acute failure. This outline will address an approach to the patient with severe hepatic disease undergoing non-liver transplant surgery. It will focus on the manifestations of organ dysfunction, pharmacology of anesthetic agents and selected aspects of anesthetic preparation and perioperative management.

THE HEPATIC CIRCULATION

Anatomy

The hepatic circulation is intimately associated with that of the rest of the gastrointestinal tract. The hepatic artery is derived from the celiac trunk, the first major branch of the abdominal aorta, and provides only about a third of the total blood flow of the liver. The celiac trunk provides the arterial supply to the foregut (stomach, spleen, duodenum); the superior mesenteric artery supplies the midgut (jejunum and ileum) and the inferior mesenteric artery the hindgut (colon and rectum). These organs all drain into the portal vein, which bathes the liver and provides two thirds of its circulation.

Hepatic Blood Flow Regulation

Hepatic blood flow is intrinsically regulated by a phenomenon known as "reciprocity of flow." The oxygen delivery (DO_2) from the hepatic artery (high saturation, lower flow) normally balances that of the portal vein (low saturation, higher flow). A decrease in hepatic artery flow is balanced by an increase in portal vein flow, to maintain DO_2 from each. Reciprocity of flow is impaired by anesthesia and lost in cirrhosis.

Autoregulation – so important at maintaining blood flow over a wide range of perfusion pressure in the brain, heart and kidney – does not exist in the portal circulation, which is perfusion pressure dependent. Vascular adrenergic receptors do play an important role in mediating hepatic and portal blood flow. Alpha receptors are distributed throughout the hepatic and portal systems, so sympathetic activation causes both hepatic artery and portal vein constriction. However, the portal circulation is devoid of β_2 receptors, so the potential benefit of β_2 receptor-induced arterial vasodilation (e.g., with dobutamine) is realized in the hepatic artery only. Dopaminergic receptors are distributed throughout the hepatic artery and portal vein, so dopaminergic agonists promote both hepatic and portal blood flow. This may or may not be beneficial (see below).

Portal constriction is induced by sympathetic stimulation, hypoxemia and hypo- and hypercarbia. In patients with severe liver disease it is prudent to ensure adequate anesthesia, intravascular volume and cardiac output, and to maintain adequate oxygenation and normocarbia.

Pharmacologic Protection

An increasing number of pharmacologic agents have been studied as agents that potentially provide liver protection during ischemia-reperfusion injury. These include vasoactive agents that promote portal flow (β-adrenergic agents, dopaminergic agents, prostaglandins); enhance liver regeneration (pentoxifylline, ciprofloxacin) and anti-oxidants (N-acetyl cysteine, NAC). Animal data have been encouraging, and in some centers NAC is added to the preservative solution or infused after high-risk liver transplantation. However, as yet there are no prospective human trials that have confirmed a benefit.

Promotion of portal vein flow is not always beneficial. In a model of hemorrhage-induced splanchnic ischemia in dogs, infusion of fenoldopam, a selective dopaminergic-1 agonist, attenuated the sympathetic splanchnic vasoconstrictor response and restored portal blood flow to near baseline. However, in a human study in patients with alcoholic cirrhosis and ascites, infusion of fenoldopam resulted in mild hypotension,

increased plasma norepinephrine and renin, and increased portal pressure, presumably due to increased mesenteric blood flow.

SYSTEMIC MANIFASTATIONS OF LIVER DISEASE

Ascites, Fluid, and Electrolyte Imbalance

Hypoalbuminemia and portal hypertension combine to induce ascites and intravascular hypovolemia. This triggers secondary hyperaldosteronism, with sodium and water retention and potassium excretion. The result is hypokalemic metabolic alkalosis, generalized edema (anasarca) and worsening ascites.

Ascites elevates the diaphragms and decreases functional residual capacity (FRC), resulting in basal atelectasis and hypoxemia. Tense ascites may increase intra-abdominal pressure to the extent that venous return and renal blood flow are decreased. Spontaneous bacterial peritonitis occurs in about 10% of patients. It is important to distinguish this from surgical peritonitis and avoid unnecessary (and potentially devastating) exploratory laparotomy.

The administration of loop diuretics to treat edema and ascites may simply exacerbate intravascular hypovolemia and hypokalemia and worsen hepatic perfusion. The specific aldosterone antagonist spironolactone is most effective in maintaining a modest potassium-sparing diuresis. However, it acts through intracellular protein induction so that its onset and offset are slow (2–3 d), and its potassium-sparing effect in acute renal insufficiency can provoke acute hyperkalemia.

Metabolic alkalosis worsens hepatic encephalopathy by nonionic diffusion trapping. With a decrease in extracellular hydrogen ion concentration, ammonium (NH_4^+), which is polarized and lipid insoluble, is converted to ammonia (NH_3) which is nonionic and crosses lipid membranes. Treatment consists of administration of potassium chloride with careful volume repletion. Refractory alkalosis has been corrected by the central venous administration of dilute (0.1N) hydrochloric acid.

Gastrointestinal Dysfunction

All patients have the potential for active viral hepatitis (A, C, D). Hepatic encephalopathy is associated with anorexia, hiccups, nausea and vomiting. As in uremia, gastric emptying is delayed and increases the risk of regurgitation and aspiration during anesthetic induction. This risk is exacerbated by severe ascites with increased abdominal pressure.

Patients with portal hypertension are at constant risk of massive hemorrhage from esophageal and/or gastric varices. However, there is also an increased risk of peptic ulcer disease, which must be considered as a potential source when gastrointestinal bleeding occurs.

Hepatorenal Syndrome

The term hepatorenal syndrome is often used to refer to any degree of renal insufficiency that occurs in the presence of liver failure. It is in fact an advanced, resistant prerenal syndrome, a form of vasomotor nephropathy, characterized by severe prerenal oliguria, low urine sodium ($\leq$10 mEq/L) and progressive azotemia.

The syndrome is seen with severe obstructive jaundice (total bilirubin >8 mg/dL) or hepatic failure. Bile salts bind endotoxin in the gut, and their absence allows access of endotoxin into the portal circulation. Because of portasystemic shunting and hepatic Kupffer cell dysfunction, endotoxin readily enters the systemic circulation and reaches the kidney. There it induces renal vasoconstriction and intense activation of renal tubular salt and water retention.

Acute tubular necrosis (ATN) may complicate liver failure independently of, or concomitant to, the hepatorenal syndrome. Endotoxin also has direct nephrotoxic effects. Tense ascites exacerbates renal dysfunction by increasing renal vein pressure, which impairs glomerular filtration. Variceal bleeding with hemorrhagic shock is one of several insults that may induce ischemic ATN.

As previously stated, in advanced liver failure the BUN remains low (<10 mg/dL) even in the presence of gastrointestinal bleeding or acute renal failure. There is impairment of the hepatic arginine cycle that converts urea to ammonia. Creatinine production is low in cachectic liver failure patients and serum creatinine often underestimates the severity of decrease of GFR. Accurate estimation of GFR and renal reserve may require measurement of creatinine clearance.

Hyperdynamic Circulation

Severe liver disease is characterized by a hyperdynamic circulation with a fixed low SVR. The vascular resistance is lowered by countless tiny arteriovenous shunts in the skin (spider nevi, palmar erythema), gastrointestinal tract and lung. Patients tend to have chronic low systemic arterial pressure. Circulatory reserve is impaired and decompensation and shock occurs rapidly with hypovolemia, sepsis or myocardial ischemia.

Alcohol-induced cirrhosis may be accompanied by alcoholic cardiomyopathy, with a predilection to cardiac arrhythmias, in which thiamine deficiency may play a contributory role.

Respiratory Failure

The hepatopulmonary syndrome describes the phenomenon of hypoxemia refractory to increased inspired oxygen fraction found in some patients with advanced liver failure. It is caused by intrapulmonary shunting through arteriovenous anastomoses, and may be associated with reactive or fixed pulmonary hypertension.

All patients with severe liver disease are at high risk of perioperative pulmonary complications, especially pneumonia. The combination of ascites. elevated diaphragms, and hypoalbuminemia predisposes to pleural effusions, atelectasis and pulmonary edema. Aspiration risk increases with worsening hepatic encephalopathy.

Hematologic Abnormalities

Liver failure patients become coagulopathic for many reasons. However the most consistent is Factor VII deficiency as a consequence of impaired hepatic synthesis and impaired gastrointestinal vitamin K absorption. Prolongation of the prothrombin time (PT) with increased International Normalized Ratio (INR) is an important marker of hepatic synthetic dysfunction, and an independent predictor of perioperative risk. Thrombocytopenia (platelet count 50–75 k) is commonly found, chronically with hypersplenism in portal hypertension, and acutely with gastrointestinal bleeding or DIC.

Factor V deficiency is a sensitive marker of acute liver dysfunction, and has been used as such after orthotopic liver transplantation.

Dysfibrinogenemia (production of an abnormal fibrinogen) occurs in advanced liver failure, and implies that fibrinogen function is abnormal even though plasma levels may be in the normal range.

Anemia is common, via several mechanisms: acute or chronic blood loss, malnutrition, and bone marrow suppression. Chronic alcoholism may be associated with macrocytic anemia.

Nutritional-Metabolic Problems

Loss of glycogenesis (hepatic glycogen synthesis) removes the ability to regulate blood glucose and patients become "poikiloglycemic" – that is, blood glucose becomes dependent on exogenous administration. Hypoglycemia (blood glucose <100 mg/dL) is almost pathognomonic of acute hepatic failure or end-stage liver disease.

Loss of hepatic albumin synthesis, protein malnutrition and the catabolic effects of hepatic failure lead to depleted lean body mass, hypoalbuminemia, and low colloid oncotic pressure (COP). This exacerbates ascites, anasarca and pulmonary edema. Loss of lean body mass also impairs normal immune and healing mechanisms. As a consequence, patients are at high risk of nosocomial and opportunistic infections, wound dehiscence, fistulas and bedsores.

Neurologic Complications

Hepatic encephalopathy is the most important neurologic complication of liver failure. Although elevated arterial ammonia (normal upper limit: 35 mg/dL) is usually associated with abnormal CNS function, it is generally accepted that it is merely a marker of disordered protein metabolism. Encephalopathy is probably caused by a variety of peptides, mercaptans and false or depressive neurotransmitters. Examples of the latter include octopamine, a catecholamine formed from phenylalanine as a consequence of a block in the synthetic pathway of the normal neurotransmitter, norepinephrine. An aromatic amino acid, tryptophan, also accumulates and is the precursor of 5-hydroxy-tryptamine (serotonin), a potent neurodepressor transmitter.

Hepatic encephalopathy may be graded as follows:

Grade 1: confabulation, constructional apraxia (loss of graphic ability)
Grade 2: drowsiness, asterexis, confusion
Grade 3: stupor
Grade 4: coma

Fulminant hepatic failure rapidly leads to hepatic coma. Breakdown of the blood-brain barrier results in acute cerebral edema, the most important determinant of outcome.

In patients with chronic liver disease, acute encephalopathy may be precipitated by a number of factors, including hypovolemia (e.g., excessive loop diuresis), gastrointestinal bleeding, surgery or infection. Another important precipitant is hypokalemic metabolic alkalosis. In an alkalotic milieu, ionized hydrophilic ammonium (NH_4^+) converts to non-ionized lipophilic ammonia (NH_3), which crosses the blood-brain barrier (nonionic diffusion trapping).

Alcoholic cirrhosis may be associated with alcohol-induced encephalopathy (thiamine deficiency), Wernicke's encephalopathy (oculomotor palsy, cerebellar ataxia), and/or Korsakoff's psychosis (amnesia, confabulation).

Pharmacologic Impact of Liver Disease

Most IV anesthetic agents are lipid-soluble and non-ionized, and undergo hepatic biotransformation to active or inactive water-soluble metabolites, which are then excreted in the bile or the urine. Lipid insoluble, highly ionized drugs (e.g., some neuromuscular blocking agents) are directly excreted by the kidney. Hepatic disease alters anesthetic and parenteral drug clearance by several mechanisms. They include decreased organ blood flow (i.e., decreased drug delivery), increased unbound free fraction of highly protein-bound drugs (hypoalbuminemia or acidosis) and decreased enzymes and transport processes that irretrievably remove the drug from the blood.

The duration of action of many drugs administered by bolus or short-lived infusion is dependent on redistribution, not elimination. Their loading doses may not require to be decreased unless unbound free fraction is increased or there is known to be a greater pharmacodynamic effect. However, maintenance doses can accumulate and should be reduced accordingly.

Liver disease alters drug pharmacodynamics even if pharmacokinetics are not changed. Patients are often debilitated, with depleted lean body mass.

Table 1. Drugs Independent of Hepatic Function for Elimination. These Drugs Undergo Enzymatic or Spontaneous Breakdown in the Blood

Drug	Mode of breakdown
Succinylcholine	Pseudocholinesterase
Esmolol	Red cell esterase
Remifentanil	Nonspecific esterases
Cisatracurium	Hofmann elimination

Respiratory depression is much more likely with opioid or volatile anesthetic agents. Therefore consideration should be given to reducing all drug dosages by 25–50%.

Drugs Independent of Liver and Renal Function for Elimination

Examples. succinylcholine, esmolol, cisatracurium, remifentanil.

These drugs undergo enzymatic or spontaneous breakdown in the blood (Table 1). Accumulation is unlikely, but altered pharmacodynamic responses should be anticipated.

Drugs with Increased Unbound Fraction in Hypoalbuminemia

Examples. thiopental, methohexital, diazepam.

In the presence of hypoalbuminemia associated with chronic renal or liver failure, these drugs have increased free or active fraction. Doses should be decreased 20–50%, depending on the degree of hypoalbuminemia.

Drugs Predominantly Dependent on Hepatic Biotransformation

Examples. lidocaine, all benzodiazepines, all opioids, dexmedetomidine, most nondepolarizing muscle relaxants (except cisatracurium).

These drugs should be restricted or used with care in hepatic failure. Drugs whose metabolism is dependent on the cytochrome oxidase (CP_{450}) system (e.g., diazepam, midazolam) are much more sensitive to liver dysfunction than those that undergo simple glucuronide conjugation (e.g., lorazepam, propofol). Lidocaine is so dependent on hepatic biotransformation that its metabolism to its primary metabolite, methylglycinexylydide (MEGX), is used as a sensitive indicator of liver function and reserve. Cumulative lidocaine toxicity with local or regional anesthesia, or continuous infusion, presents a special risk in patients with end-stage liver disease.

Volatile Anesthetic Agents

All volatile anesthetic agents have the potential to decrease hepatic blood flow, depending on their effect on the central circulation. Agents with potent negative inotropic effects such as halothane or enflurane, may decrease blood flow by 30–50%.

Table 2a. Child-Turcotte-Pugh Score for Cirrhosis

Parameter	1	2	3
Serum bilirubin (mg/dL)	<2	2–3	>3
Serum albumin (g/dL)	>3.5	3–3.5	<3
PT (sec > control)	1–4	4–6	>6
CNS (coma grade)	Normal	Confused (1–2)	Coma (3–4)
Ascites	None	Easily controlled	Poorly controlled

Table 2b. Child-Turcotte-Pugh Class and Preoperative Risk Assignment

Class	A	B	C
Score	5–6	7–9	10–15
Risk	Minimal	Moderate	Severe
Operative Mortality	0–10%	4–31%	19–76%

Hepatotoxic Effects

The potential for hepatotoxicity appears to be somewhat related to the extent of hepatic metabolism of the volatile agent. About 20% of halothane is eliminated by hepatic biotransformation, whereas only 2% of enflurane and sevoflurane, and 0.2% of isoflurane are metabolized by the liver.

Mild hepatotoxicity (transient modest elevation of liver enzymes) probably occurs in about 1 in. 700 cases, and is related to injury caused by reductive metabolites, which are more likely to be formed in an hypoxic milieu.

Fulminant hepatic necrosis ("halothane hepatitis") is a devastating injury with a high mortality. It appears to be induced by immune sensitization to the trifluoroacetylated products of oxidative metabolism (CP_{450} 2E1). The true incidence is difficult to assess. The 1966 National Halothane Study concluded that it occurred in 1: 35,000 exposures to halothane. Subsequent large scale studies have suggested an equivalent risk of hepatic injury with enflurane and isoflurane, but that the actual incidence is considerably lower. Unfortunately, any occurrence of postoperative jaundice or elevation in liver enzymes tends to be labeled "halothane hepatitis" by our surgical and medical colleagues. Patients appear to be genetically predisposed, and the risk may be enhanced by the concomitant use of agents that induce mixed function oxidases, such as acetaminophen. The most important risk factor is re-exposure to halothane within two weeks. There appears to be cross-reactivity with other agents, e.g., a patient with a history of halothane-induced hepatotoxicity may develop recurrent injury on exposure to isoflurane.

PREOPERATIVE EVALUATION

Child-Turcotte-Pugh Score

The most widely used tool for assessment of risk in patients with cirrhosis is the Child-Turcotte-Pugh Classification (Table 2a and 2b), which is reasonably

Table 3. High Risk Procedures in Cirrhotic Patients Independent of Child-Turcotte-Pugh Classification

Procedure	Risks and complications
Emergency surgery (laparotomy)	Liver failure, 25% mortality rate
Prior abdominal surgery	Neovascularization: bleeding
Cardiopulmonary bypass	Severe coagulopathy and bleeding, high mortality
Ileostomy, colostomy	High incidence of ascitic leaks
Cholecystectomy	Portal hypertension, coagulopathy: bleeding from gall bladder bed
Hepatic tumor resection	Bleeding, liver failure

Table 4. Contraindications to Elective Surgery in Liver Disease

1. Acute viral hepatitis
2. Acute alcoholic hepatitis
3. Fulminant liver failure
4. Chronic active hepatitis (symptomatic)
5. Child's Class C cirrhosis
6. Severe coagulopathy
   a) Prothrombin time >3 sec above control, not correctable
   b) Platelet count <50 k/mm3
7. Comorbidity:
   a) Congestive heart failure
   b) Acute renal failure
   c) Hypoxemia

predictive of perioperative mortality. A score of 1–3 is ascribed based on the degree of abnormality of five parameters, including bilirubin, albumin, PT, grade of encephalopathy and ascites. Thus, the minimal score is 5 (Child's A) and the maximum score is 15 (Child's C). In general, patients with a Child's A score present minimal risk for elective surgery, which should proceed; with Child's C it is contraindicated. Patients with Child's B criteria fall into an intermediate category and must be evaluated on an individual basis. However, regardless of the Child's classification, a prothrombin time prolonged >3 sec above control that does not correct with Vitamin K is an important predictor of poor outcome. Other independent risk factors are listed in Table 3.

Meld Score

More recently the MELD (Model for End-stage Liver Disease) Score has emerged as an important predictor of mortality that is used predominantly to prioritize patients for orthotopic liver transplantation. It is based on a complex nomogram that incorporates exponentials of the bilirubin, serum creatinine and INR.

Contraindications to elective surgery in liver disease are detailed in Table 4.

PREOPERATIVE PREPARATION

Medical Management

It may be helpful to drain tense ascites preoperatively – this will decrease diaphragmatic pressure and allow more easy positioning of the patient. It must be done with caution because of the risk of inducing acute intravascular hypovolemia, hypotension and further liver injury.

Many patients are on the aldosterone antagonist, spironolactone, which promotes sodium excretion and potassium retention. It is long acting and could exacerbate hyperkalemia in the presence of acute renal insufficiency or failure. If possible, spironolactone therapy should be discontinued 3 to 4 days before surgery.

An attempt to correct factor VII deficiency and prolonged prothrombin time should be made with parenteral Vitamin K and/or fresh frozen plasma (FFP). However, these may be largely ineffective in patients with severe liver damage, and administration of several units represents a substantial volume load.

Precipitating Factors of Encephalopathy Should Be Treated or Removed by Protein Restriction, Lactulose and/or Neomycin

Patients with end-stage renal disease have a very high incidence of hepatorenal syndrome and are exquisitely sensitive to small decreases in intravascular volume. Steps should be taken to ensure adequate preoperative hydration in these patients, i.e., maintenance saline infusion during preoperative fasting. Pharmacologic renal protection (low dose dopamine, furosemide infusion, fenoldopam) is frequently used during orthotopic liver transplantation. Although these agents are effective at inducing diuresis, there are few if any prospective data that suggest that they decrease the risk of perioperative renal injury.

Transjugular Intrahepatic Portasystemic Shunt (TIPS)

The TIPS procedure is being used with increasing frequency especially in patients who are candidates for orthotopic liver transplantation. It decompresses the portal system, relieves severe ascites, decreases the risk of variceal bleeding, and in some patients improves renal perfusion and hepatorenal syndrome. The procedure is performed in the invasive radiology suite. A metallic shunt is passed via the internal jugular route into the hepatic vein, and thence driven through the liver until the portal vein is reached and pressure gradient drops. Acute risks include bleeding, acute heart failure from sudden increase in right atrial filling, and endotoxemia from portasystemic shunting. There is also an increased risk and susceptibility to encephalopathy.

Immediate Preoperative Preparation

Omit oral premedication except for aspiration prophylaxis. If necessary, give small doses of IV sedation

in induction room or operating room, but always under direct observation.

Use universal precautions and asepsis throughout; all staff should have been vaccinated against hepatitis B whether or not the patient is known to be a carrier.

There should be a low threshold for using invasive monitoring for any surgical procedure liable to involve fluid shifts. Patients with hepatorenal syndrome are at very high risk of perioperative acute renal failure and intravascular volume status is difficult to assess because of ascites and anasarca.

Considerations for positioning and avoidance of hypothermia are as for chronic renal failure. Tense ascites adds an additional degree of difficulty.

ANESTHETIC PLANNING AND MANAGEMENT

Anesthetic Plan

Regional anesthesia may help to preserve hepatic blood flow if blood pressure and cardiac output are maintained. However, the common presence of coagulopathy, ascites, and encephalopathy limit its application.

Drug handling is extremely variable. Altered pharmacokinetics are a consequence of a large volume of distribution but markedly impaired hepatic elimination. Thus, the loading dose requirement for certain drugs may be high, but emergence is substantially delayed. This applies for example to rocuronium, whose onset of action is delayed by an enlarged volume of distribution in patients with severe liver disease. Moreover, even though its elimination kinetics are unaltered, the time to recovery is prolonged.

Doses of all sedative agents should be substantially decreased in severe liver disease.

Anesthetic Induction

Management of anesthetic induction is similar to chronic renal failure, and should incorporate preoxygenation, adequate fluid loading and aspiration precautions.

Succinylcholine apnea has been rarely reported in patients with severe liver dysfunction and is related to very low levels of plasma cholinesterase. Metabolism of cisatracurium is independent of liver function and it is the neuromuscular blocker of choice. A metabolite, laudanosine, may accumulate in liver disease. In dogs, high laudanosine levels are associated with electrical seizure activity, but these have never been encountered in humans nor reported in patients.

Anesthetic Maintenance

All volatile anesthetic agents decrease hepatic blood flow based on their effects on the central circulation, but this can be overcome by appropriate hemodynamic management. Hypercarbia and hypocarbia decrease portal flow and should be avoided. Opioids, with the notable exception of remifentanil, may accumulate and delayed emergence should be anticipated if they are used. Remifentanil pharmacokinetics are unchanged even in the presence of severe liver disease, but patients are more sensitive to its pharmacodynamic effect in suppressing ventilatory drive.

The short duration of propofol effect is related to its high lipid solubility and rapid distribution out of the CNS. Thus, it remains a relatively short-acting drug even in patients with advanced cirrhosis. However this advantage is offset by its effects on the circulation, which include myocardial depression, inhibition of reflex tachycardia and vasodilation, keeping in mind that these patients are already hypotensive at baseline.

The anesthesiologist should anticipate intraoperative hypoxemia (ascites, hepatopulmonary syndrome), bleeding (coagulopathy) and oliguria (hepatorenal syndrome).

An important intraoperative consideration in the anesthetic management of partial hepatectomy or liver transplantation is the avoidance of excessive volume loading. Hepatic venous congestion increases venous oozing and markedly increases intraoperative blood loss, perhaps the most important determinant of outcome after hepatic resection. A fluid restrictive approach during hepatic resection has been shown to decrease intraoperative blood loss. Hepatic swelling can also irreparably injure the newly transplanted liver. Although it is essential to maintain intravascular volume and hepatic perfusion, efforts should be made to keep the CVP $\leq$10 mm | Hg in patients with normal cardiac function.

Emergence and Postoperative Care

Anesthetic emergence may be delayed and complicated by vomiting and aspiration, hypotension, respiratory depression and acute respiratory failure. Patients should have their trachea extubated only when they are fully awake to reduce the risk of aspiration. Similarly, a short period of postoperative mechanical ventilation allows controlled emergence, avoids reversal agents, and facilitates evaluation of neurologic and ventilatory function prior to extubation.

Potential postoperative problems include bleeding, oliguria, encephalopathy, acute respiratory failure, sepsis, wound dehiscence and acute hepatic failure.

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Integrating Regional Anesthesia into Postoperative Pain Management in Children: An Intensive Review

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The use of regional anesthesia in children and adolescents has seen resurgence in the past decade due to innovative methods described as well as newer technology that can facilitate easy placement of blocks. An explosion of material available on the web as well as standard textbooks incorporating DVD technology to demonstrate the placement of these blocks have resulted in a wider exposure of anesthesiologists to pediatric blocks. This review course will discuss the use of common blocks in pediatrics with greater emphasis on dosing as well as technique. Teaching regional anesthesia for use in children is still lacking and greater effort should be made to add regional anesthesia techniques as part of the required curriculum in children in training programs. The controversy about the use of regional techniques in children under anesthesia is not much of an issue although there have been multiple reports with complications associated with regional techniques in adults under general anesthesia.[1] This case report was followed by vigorous discussions in the pediatric anesthesia circles followed by an editorial that accompanied the article in *Regional Anesthesia and Pain Medicine*.[2] Other new data showing the efficacy of monitoring injection pressures may have significant implications in pediatric anesthesia.[3] A large prospective database from the French language speaking areas demonstrated a very low incidence of regional anesthesia related complications in children.[4] Although the field of regional anesthesia has recently exploded with ultrasound guided blocks, the use of this technique is not so common yet in regional techniques for children.[5]

EQUIPMENT AND TECHNOLOGY

Nerve stimulation is still commonly used for regional techniques in children. The stimulation techniques used are very similar to adult nerve stimulation. There is one area that may be more commonly used in children and this includes the use of surface mapping in children. Using higher amperage, (usually about 7 mA), the skin over the area of the nerve can be adequately stimulated to produce the desired response to nerve stimulation.[6] This is often used in the absence of ultrasound equipment for localization of the nerves. This prevents repeated needle entries prior to nerve localization. Nerve stimulation can be used for caudal blocks as well as epidural catheter placement using the Tsui technique. This can facilitate the placement of the catheter into higher dermatomal level with greater accuracy.[7,8] The introduction of ultrasonography (US) into clinical practice in pediatrics has greatly enhanced the performance of regional anesthesia in children.[9] The availability of US machines in most medical centers and the knowledge gained from the published material should enhance the use of US in clinical practice. Regional techniques including the use of epidural analgesia can improve the use performance of these blocks. The use of US guidance can also reduce the volume of local anesthetic solution needed for these blocks and hence may pose an excellent risk benefit ratio particularly for children.[10]

LOCAL ANESTHESIA SOLUTION

Bupivacaine is commonly used local anesthetic solution in pediatric practice in North America. The pharmacokinetics of bupivacaine has been adequately studied in children.[11] Dosing guidelines for local anesthetic are strictly followed using a mg/kg basis rather than a total volume dose.[12,13] The use of ropivacaine and levobupivacaine in Europe and Asia seems to have a better safety profile compared to bupivacaine although the risk of toxicity with IV injection remains.[14]

CENTRAL NEURAXIAL BLOCKS

Caudal Blocks

The most common block used in children is a caudal block.[15] This is uniformly taught at most training programs in North America and Europe. The technique is simple and requires very little equipment other than a needle and local anesthetic solution. After palpation of the sacral hiatus, the needle is advanced until a "pop" is felt. This denotes the placement of the needle in the caudal epidural space. A gentle loss of resistance can be felt as the caudal space is entered. Local anesthetic solution is injected in a graduated manner to a total volume of 1 mL/kg. This provides postoperative analgesia for most surgeries below the umbilicus for up to 5 hours with local anesthetic solution alone. The addition of additives to the caudal solution does not uniformly seem to improve the

Table 1. Dose of bupivacaine in the epidural space (13)

Age	Bolus dose	Continuous infusion
Infants	2 mg/kg	0.2 mg/kg/h
Children	3 mg/kg	0.3 mg/kg/h
Older children	4 mg/kg	0.4 mg/kg/h

duration of analgesia in infants and children.[16] It is imperative to monitor the ECG to look for any "peaked T-waves" as a sign of intravascular placement if epinephrine is used in the local anesthetic solution.[17] Newer techniques including the use of stimulating technique as described by Tsui[8] or more recently an ultrasound-guidance technique[18] may lead to accurate localization of the caudal space.

EPIDURAL CATHETERS

This technology for use in pediatrics has existed for more than a couple of decades. The limiting factor to their routine use has been the availability of smaller needles and catheters for use in children. Loss of resistance with saline is preferred in neonates and infants due to the potential of introducing a large bolus of air causing air embolism.[19] Stimulation techniques[7] as well as ultrasound guidance[18] has been recently introduced for placement of epidural catheters in children. This may provide a more accurate method for catheter placement. Dosing of local anesthetic for continuous infusion has to be carefully titrated based on body weight and age. A rule of thumb for local anesthetic dosing is the 4, 3, 2 rule (Table 1).[20] T1

A dedicated pain treatment service with adequate and frequent follow up of patients is required to facilitate the use of regional anesthesia techniques in children. It is important to stress the importance of moving patients on their sides so that they do not develop heel sores following regional anesthesia. Thoracic epidural analgesia can be placed successfully in children.[21] Patient controlled epidural analgesia can be very rewarding especially in older children and adolescents for managing postoperative pain and is a routine part of our treatment modality for children over 6 years of age or those with the cognitive ability to discern pain.[22]

PERIPHERAL NERVE BLOCKS

A variety of peripheral nerve blocks are utilized in children (Table 1). The use of peripheral blocks in routine practice is increased due to the power of the Internet, the greater exposure to hands-on teaching workshops (NYSORA, ASA, IARS, ASRA), and the resources available for patients and families to check the potential possibilities for pain control. We offer a variety of regional techniques in our practice. A sampling of the variety of nerve blocks will be elucidated in the following paragraphs. A full detailed review of these blocks is found in standard textbooks (*Modern Regional Anesthesia*, Hadzic A, 2006).

Head and Neck Blocks

A variety of different blocks are performed in children for various surgical procedures. The sensory supply to the face is supplied by the terminal branches of the trigeminal nerve, (V1, V2, and V3). These supply the entire frontal face and some of the temporal aspects of the face and scalp. The occipital nerve and the superficial cervical plexus supply the neck and the posterior portion of the ear.

Supraorbital Nerve

The V1 branch of the trigeminal nerve provides the sensory supply to the anterior portion of the scalp, anterior to the coronal suture. The nerve exits the skull through the supraorbital foramen. Blockade of the nerve is easy as it exits the supraorbital foramen and can be easily performed using 0.5 mL to 1 mL of local anesthetic solution injected subcutaneously at the level of the supraorbital foramen. We utilize this block for frontal craniotomies, scalp lesion excisions, and for minor surgical procedures on the anterior portion of the scalp.[23,24]

Infraorbital Nerve

This is the terminal part of the maxillary division of the trigeminal nerve that exits the infraorbital foramen at the inferior border of the orbital rim.[25,26] The nerve can be easily blocked using an intraoral approach (our preference), or an extraoral approach. This is useful for patients who have surgery for cleft lips[27] or endoscopic sinus surgery.[26,28] After eversion of the upper lip, a 27-G needle is inserted into the oral cavity at the subsulcal plane and after careful aspiration 0.5 mL of local anesthetic solution is injected into the area of the infraorbital nerve. This provides adequate analgesia for postoperative pain control.

N of Arnold

This is the auricular branch of the vagus. The nerve is located behind the tragus and is easy to block for myringotomy tube placement. We have just completed a randomized controlled trial comparing the use of this block to IV injection of fentanyl and demonstrated equianalgesic response to pain in the postoperative period.

Superficial Cervical Plexus

The C2-C4 branches of the cervical plexus form the superficial cervical plexus. This winds around the sternocleidomastoid and has 4 branches, the great auricular, which supplies the post-auricular area; the transverse cervical that supplies the anterior cervical area and the thyroid; the supraclavicular that supplies the sensory supply to the shoulder; and the lesser occipital, which along with the greater occipital supply the posterior occiput. The nerves can be easily blocked in the neck using a subcutaneous injection at

the level of the cricoid and at the posterior border of the sternocelidomastoid. The injection is superficial and should create a wheal at the site of injection. We use this block routinely for patients undergoing tympanomastoid surgery[29] and for thyroid surgery[30] and vocal cord surgery.[31]

Occipital Nerve Block

The occipital nerve, a branch of the cervical root, is noted on either side of the midline juxta to the occipital artery. After palpation of the occipital artery, the nerve is blocked with 1 mL of local anesthetic solution injected on either side of the occipital protruberance. This is useful for posterior fossa craniotomies as well as in patients with occipital neuralgia.

UPPER EXTREMITY BLOCKS

The brachial plexus is blocked for surgery involving the upper extremity.[32] I will discuss mainly the indications for the variety of approaches to the brachial plexus in children

- *Interscalene*: This is very rarely performed in children. However this block can be easily performed with greater safety in children using ultrasound guidance.
- *Supraclavicular block*: The supraclavicular block is more often used in children and can be easily performed with the aid of ultrasound guidance. This is very useful for patients who require fracture reductions.[33]
- *Infraclavicular*: This technique is often used in our practice for children who require long-term catheter placement.
- *Axillary block*: The axillary approach used to be the most commonly used technique in children.[34] However with the advent of US-guided blocks, other approaches to the brachial plexus are commonly used now. However, in our practice we find that the performance of the axillary block under US guidance has led to specifically blocking nerves for various surgical procedures based on their nerve distribution.

LOWER EXTREMITY BLOCKS

Lower extremity blocks in children are mainly involving the femoral and sciatic nerve blocks.

- *Femoral nerve*: The femoral nerve is perhaps the most common nerve blocked in children. The femoral nerve, a branch of the lumbar plexus can be easily blocked in the femoral crease below the inguinal ligament. Surface mapping can be easily carried out at this area.[6] The indications for femoral nerve blocks include lower extremity surgery including fracture reductions.[35,36] US guidance can be used for provision of this block with ease.[5] We also use the femoral approach for placement of catheters for children undergoing knee athroplasty or ACL repair. More recently, we discharge patients home on these catheters after surgery.
- *Lateral femoral cutaneous nerve block*: This can be used for patients who are undergoing muscle biopsies[37] as well as in combination with a femoral nerve blocks for pin removal and plate removal from the lateral aspect of the femur.
- *Sciatic nerve block*: This is commonly used in children for foot surgery. We have resorted to the use of peripheral block techniques and have shied away from central neuraxial blocks if the surgery involves one extremity. This results in lower incidence of nausea and vomiting and urinary retention.[38] A posterior popteal fossa approach is preferred to the lateral approach in children. More recently a subgluteal approach has been used in children for placement of catheters. The use of US guidance has decreased the incidence of complications while improving the ability to place catheters.[39]

TRUNCAL BLOCKS

The use of truncal blocks in children is more frequent than in the adult population. Although there is limited research in the utilization of these blocks, we feel that the use of truncal blocks in the routine postoperative care of children may far exceed the use of other blocks in routine practice.

- *Ilioinguinal nerve blocks*: The ilioinguinal and iliohypogastric nerves are most commonly performed in children undergoing hernia repair. The nerves are located in the facial plane between the internal oblique and the transverse abdominus muscle. They are derived from T-10 to T-12 thoracic nerve roots. The usual technique of utilizing a "pop" method has been replaced with US guidance, which affords easy visibility of the nerve and can be used for localizing the ilioinguinal and iliohypogastric nerves.[40] Newer pharmacodynamic studies have also reduced the need for large volumes of local anesthetic solution for these blocks.[10]
- *Rectus sheath blocks*: The rectus sheath is a compartment that is enveloped between the rectus abdominus muscle and the posterior rectus sheath. The thoracic intercostals nerves T-7 to T-9 run in this space to supply the sensory fibers to the anterior abdominal wall especially around the umbilicus. This can be used effectively for providing analgesia to the umbilicus. A newer US-guided imaging technique is used for localizing the exact position of this space and can facilitate easy placement of this block.[41]

Table 2. Local Anesthetic Volume for Common Blocks

Block	Volume	Indication
Supraorbital	0.5 mL	Scalp surgery
Infraorbital	0.5 mL to 1 mL	Cleft lip repair
N of Arnold	0.2 mL	Myringotomy tube
Greater palatine nerve	0.5 mL	Palate surgery
Brachial plexus	0.2 mL/kg	Upper extremity surgery
Femoral nerve	0.1 to 0.2 mL/kg	Femur surgery/ ACL
Sciatic nerve	0.2 mL/kg	Foot surgery
Rectus sheath	0.1 mL/kg	Umbilical hernia repair
Ilioinguinal nerve block	0.1 mL/kg	Hernia repair

PERIPHERAL NERVE BLOCK CATHETERS

The use of peripheral nerve catheters has recently been introduced in pediatric practice.[39] The use of perineural catheters along with methods to secure them will be discussed in this workshop. Commonly used perineural catheters in children include sciatic, femoral and infraclavicular catheters.

CONCLUSION

Regional anesthesia in children can be effectively carried out with proper guidance and application. The major advantage with the use of regional anesthesia in children is the avoidance if the use of opioids for postoperative pain control. A formal teaching program to facilitate the demonstration and teaching of these blocks is needed to improve the utilization of regional anesthesia in children.

T2

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Infections and Anesthesiologists

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This abstract will review two deadly infections that are rare, avian influenza A and extremely resistant tuberculosis. However, given that these infections proliferate in the airways of patients who often require endotracheal intubation, these infections are of grave risk to anesthesiologists and other health care personnel exposed to airway secretions. The other two infections discussed, MRSA and *C. difficile* are much more common and most health care workers will be exposed to these bacteria. These bacteria are found on patients as well as on the belongings of patients and on furniture and in the environment near infected patients. All these infections can cause harm to health care providers; awareness of the details of these infections suggest that protective eyewear, N95 masks that are fitted, protective clothing, and gloves are important adjuncts to be utilized in daily routines for the safety of health care providers.

(Anesth Analg 2008;106:●●●-●●●)

RARE BUT DEADLY INFECTIONS IN THE AIRWAYS OF PATIENTS

Avian Influenza A [H5N1] Virus

The avian influenza A viruses are found in poultry in Asia, Africa, and perhaps in the Middle East.[1] The avian influenza virus that infects humans comes from birds, both from poultry and from wild birds. Migratory birds may spread H5N1 viruses to new geographic locations, but their importance as a reservoir of these viruses is not clear.[1] Despite widespread exposures to infected poultry, human disease due to H5N1 influenza A virus is rare.[1] As of December 14, 2007, there have been 340 reported cases.[1] The data regarding these cases shows that the patient's median age is 18 years and that 90% of these patients are under 40 years of age.[2] The fatality rate is 61% with the most frequent deaths in patients 10–19 years of age.[2]

The cases seem to occur in cooler months, associated with outbreaks in poultry.[3] Limited data has shown that asymptomatic or mild human influenza A infections are rare but do occur.[4]

Infection occurs after transmission of the virus from avian-to-humans; handling of sick or dead poultry during the week before the onset of the illness is the most commonly recognized risk factor.[5] Other risk factors include: slaughtering, defeathering, preparing sick poultry for cooking, playing with or holding diseased or dead poultry, handling fighting cocks or ducks, and consuming raw or undercooked poultry or poultry products.[5–8] It is believed that most of the patients were exposed to the poultry. In some limited, nonsustained cases there may have been human-to-human transmission where there was close and unprotected contact with a severely ill patient.[9,10] Respiratory secretions and all body fluids, including feces, are potentially infectious.[1] It is thought that some of the cases were due to inhalation of aerosolized infectious excreta.[1] After exposure to infected poultry, the incubation period is approximately 7 days.[1]

The pathologic process that appears to cause death is fulminant viral pneumonia.[1] The virus replicates in type 2 alveolar cells and in macrophages.[11,12] Ultimately, however, high titers of virus are detectable in the throat and in tracheal aspirates from humans infected with the H5N1 virus.[13] Ability of the virus to replicate may influence outcome; larger loads of virus were found in the throats of patients who died when compared to the loads in patients who lived.[13] Disseminated infection can clearly occur; virus has been detected in blood, cerebrospinal fluid, and in various viscera of patients who have died.[13]

Symptoms and signs include fever, cough, respiratory distress, and at times vomiting, diarrhea, leucopenia, lymphopenia, thrombocytopenia, and increased aminotransferase levels.[1] The infection can be detected by real-time reverse-transcriptase polymerase chain reaction.[14] Multiple samples should be obtained from the nose or throat; tracheal aspirates have higher viral titers and yields than specimens from the upper respiratory tract.[13]

Treatment

Early treatment with oseltamivir is recommended.[15] A higher dose of oseltamivir (i.e., 150 mg b.i.d. in adults) for 10 days has been recommended when disease progresses despite early treatment.[1]

Extensively Drug Resistant-Tuberculosis: XDR-TB

There are approximately 9 million new cases of TB in the world annually with 1.6 million deaths; over 80% of the cases occur in Asia or Africa.[16] Nine countries in sub-Saharan Africa have annual incidences in excess of 600 cases per 100,000, a burden of disease not seen since therapy has been available.[17] This increase is largely due to the AIDS epidemic in this region and the weak health care delivery systems.

Resistance to at least two major anti-tuberculosis drugs, isoniazid and rifampicin, has been called multidrug-resistant tuberculosis, MDR-TB. Approximately 425,000 MDR-TB cases occur annually worldwide, representing nearly 5% of the world's annual TB burden.[18] Treatment of MDR-TB requires a more prolonged therapy, a course of 24 months, and more expensive chemotherapy (of up to 300-fold higher costs) than non-MDR-TB and often leads to increased toxicity. When tuberculosis becomes resistant to the second-line therapy it is known as extensively drug resistant-tuberculosis or XDR-TB. Countries in Eastern Europe, the former Soviet Union, regions of China as well as sub-Saharan Africa have an increased burden MDR-TB and now XDR-TB. MDR-TB and XDR-TB are associated with very high mortalities, due to the vulnerable patient population and the problems in finding therapies that do not interact with antiretroviral agents.[19–21]

For persons infected with *M. tuberculosis*, HIV infection is the strongest risk factor for the development of active TB.[18] TB is the leading cause of death among HIV-infected persons and may accelerate the course of HIV infection, increasing the viral load in some patients.[18,22–24] In a 1996 study from New York City, 72% of HIV-infected patients with MDR-TB died during treatment, compared with 20% of MDR-TB patients without HIV; median survival was 14 months.[25] Surgery improves treatment outcomes in selected patients with MDR-TB and warrants further evaluation for XDR-TB.[18,26]

China has the greatest estimated burden of MDR-TB worldwide (~140,000 cases annually) and India has the world's highest burden of TB overall, with about 90,000 cases of MDR-TB annually.[18] Mexico has 2500 cases of MDR-TB annually. In contrast, the United States has about 121 cases of MDR-TB annually but had 15 cases of XDR-TB.[18]

TB transmission to health care providers has increasingly occurred. In Zambia, there were 8 nurses that developed TB in the 1980s and all were successfully treated. Between 1990–1996, 114 nurses died of TB at the same hospital.[18]

MORE COMMON AND LESS DEADLY INFECTIONS: MRSA AND *C. DIFFICILE*

MRSA

Hospital-acquired MRSA infections have been associated with poor patient outcomes; recently, community-acquired MRSA infections in the United Kingdom and United States are being reported to be associated with poor patient outcomes, including death.[27] Patients with community-acquired MRSA were more likely to be male and to have comorbidities than similar patients without MRSA. Furthermore, the patients with MRSA had an increased likelihood of dying within 1 year of the diagnosis.[27] The community acquired MRSA, CA-MRSA strains, have been associated with skin and soft tissue infections, bacteremia, endocarditis, pneumonia and empyema, osteomyelitis, and pyelonephritis.[28,29] Evaluating consecutive patients undergoing operative debridement for complicated skin and soft tissue infections from 2000–2006 in a Houston VA hospital, it was found that there were 288 patients with skin and soft tissue infections. About 70% of the infections were culture positive for *S. aureus* and 49% were MRSA in 2006; in contrast, in 2000 only 34% of the cultures were positive for MRSA.[30] This data suggests there has been a significant increase in CA-MRSA and suggests that precautions should be taken when touching patients' skin or fomites that have been on patients.

Not only is the incidence of MRSA increasing in communities, but there is concern that the exposure of MRSA to chlorhexidine is increasing resistance of *S. aureus* to chlorhexidine. Chlorhexidine is now routinely used as a cleansing agent on the skin of patients as well as an oral antiseptic to prevent ventilator associated pneumonia and other hospital-acquired infections.[31–34]

One hundred and twenty clinical MRSA strains were collected from the clinical microbiology laboratories in Edinburgh and were evaluated for the presence of chlorhexidine resistance genes using PCR. The isolates were also exposed to chlorhexidine for 5 minutes, and survival of the exposed bacteria was determined. There are at least 12 "biocide resistance genes" including *qacA-qacJ*, *smr*, and *norA*. These genes appear to confer resistance not only to cationic antiseptics but also to biguanides.[35] The *smr* gene encodes a protein that functions as a drug pump; the gene is often on plasmids that are <3 kb. *qacA* and *B* genes are on large plasmids, >20 kb, and mediate an energy-dependent export system. The blaZ β lactamase gene resides on a common plasmid with the *qacA*/B genes.[35]

All of the 120 MRSA isolates were mecA-positive. *qacA/B* was detected in 10 isolates (8.3%), *nor* A was detected in 44 [37%], *smr* in 53 isolates [44%] and *blaZ* in 117 [97.5%]. Only 5 isolates had both *qacA/B* and *smr*. All the isolates that had the *qacA/B* gene also contained the β lactamase transposon, blaZ, but not all the isolates with the blaZ gene contained *qacA/B*. This suggests that not all antibiotic resistant strains are resistant to biocides, but that strains resistant to biocides tend also to be resistant to antibiotics genes.[35]

C. difficile

Clostridium difficile lives as an anerobic spore, and the spores can survive on inanimate surfaces for months. Recently a study documented that *C. difficile* spores are in the air of hospital wards; indeed it appears that air vents and other surfaces are probably contaminated with *C. difficile* spores.[36] Reports have shown that the bathrooms and toilets are among the most contaminated areas in the hospital but notably this recent study documented that the *C. difficile* spores were found in the air in a ward where there had not been a patient with *C. difficile* associated

diarrhea (CDAD) for 7 weeks.[36] *C. difficile* spores do survive for less time on copper alloy surfaces suggesting that specific surfaces can discourage the survival of this pathogen possibly by forming hydroperoxides.[37] Also, it appears that many asymptomatic patients have *C. difficile* in their stool. A recent investigation documented that 51% of patients were asymptomatic carriers of *C. difficile*, and that these patients also had these organisms on their skin. Samples taken from the environment near these patients also documented environmental contamination. Previous antibiotic usage was strongly associated with asymptomatic *C. difficile* carriage.[38] All this data suggests that health care workers should assume all patients potentially carry *C. difficile* and that even touching objects inpatient's rooms can lead to contamination by *C. difficile*. Hand washing is required to get rid of *C. difficile*; alcohol washes do not eliminate the spores.

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Obstetric Anesthesia and Ewe: Update in Clinical Care

Cynthia A. Wong, MD

OBJECTIVES: By the end of this lecture, participants should be able to

- Understand the relationship between timing of the initiation of neuraxial labor analgesia and the progress of labor.
- Understand the relationship between dense epidural labor analgesia and the outcome of vaginal delivery.
- Explain the advantages and disadvantages of different methods of maintaining epidural labor analgesia: Intermittent manual bolus, continuous infusion, patient controlled analgesia with and without a background infusion, and timed-intermittent bolus injections.
- Explain the reasoning behind choice of vasopressors (ephedrine and phenylephrine) for the treatment of neuraxial-anesthesia induced hypotension during cesarean delivery.
- Understand the benefits and limits of crystalloid and colloid administration for the prevention of hypotension during spinal anesthesia for cesarean delivery.
- Understand the risks and benefits of spinal versus epidural anesthesia for cesarean delivery in women with severe preeclampsia.

(Anesth Analg 2008;106:●●●–●●●)

EARLY LABOR NEURAXIAL ANALGESIA AND THE PROGRESS OF LABOR

Multiple observational studies have found that early labor initiation of epidural analgesia is *associated* with a higher risk of cesarean delivery.[1,2] For many years, the American College of Obstetricians and Gynecologists (ACOG) recommend that women delay, *when feasible,* initiation of neuraxial analgesia until the cervix was dilated to 4 to 5 cm. As a result, many women received systemic opioid analgesia early, latent phase labor, followed by neuraxial analgesia in active labor.

An association, however, does not necessarily mean cause and effect. Randomized controlled trials have compared initiation of neuraxial analgesia to systemic opioid analgesia in early labor. Chestnut et al.[3,4] found no difference in cesarean delivery rate between nulliparas randomized to early epidural analgesia (cervical dilation between 3 and 5 cm) compared to late epidural analgesia (cervical dilation ≥5 cm, nalbuphine in early labor). Wong et al.[5] found no differences in the cesarean delivery rate in 750 nulliparas in spontaneous labor randomized to early (cervical dilation <4 cm, median 2 cm) initiation of combined spinal-epidural (CSE) analgesia compared to the control group (early systemic hydromorphone analgesia followed by epidural analgesia, median cervical dilation 4 cm): early CD rate 17.8%, late 20.7%, rate difference −2.9%; 95% CI for the difference −9.0 to 3.0%; $P = 0.31$. In a study of 449 nulliparas in spontaneous or induced labor randomized to early epidural analgesia (mean cervical dilation 2.4 cm) or early meperdine followed by late epidural analgesia (mean cervical dilation 4.6 cm) there was no difference in the rate of CD (13% vs 11%, $P = 0.77$).[6] Finally, a recent meta-analysis addressing this issue ($n = 3320$) also concluded that early labor neuraxial analgesia compared to systemic opioid analgesia does not increase the rate of cesarean delivery (OR 1.0, 95% CI 0.82–1.23) or instrumental vaginal delivery.[7] Pain control was better, and neonates of women with early neuraxial analgesia had higher umbilical artery pH and lower need for naloxone.

In a new Committee Opinion from June 2006, the American College of Obstetricians and Gynecologists (ACOG) stated that that they "previously recommended that practitioners delay initiation of epidural analgesia. . . . However, more recent studies have shown that epidural analgesia does not increase the risks of cesarean delivery . . . The fear of unnecessary cesarean delivery should not influence the method of pain relief that women can choose during labor."[8]

Pain, Request for Analgesia, and Cesarean Delivery

Taken together, these data suggest that the request for analgesia early in labor is a marker for some other risk factor for cesarean delivery. It is likely that women who request early labor analgesia have more pain than women who do not, and pain is a marker for risk of cesarean delivery. Hess et al.[9] evaluated risk factors for cesarean delivery in women who received low dose bupivacaine-fentanyl infusions for epidural labor analgesia. Three or more episodes of breakthrough pain, requiring a manual bolus by the anesthesiologist was associated with a twofold higher rate of cesarean delivery compared with women who required <3 manual bolus doses. Panni et al.[10]

evaluated the minimum effective local anesthetic concentration (MLAC: the concentration of bupivacaine (20 mL) that resulted in effective analgesia for 50% of laboring women) and found that the MLAC was higher in women who went on to have a cesarean compared to vaginal delivery. Finally, in a secondary analysis of a group of women randomized to IV meperidine patient controlled labor analgesia (PCIA), the cesarean delivery rate for women who gave themselves more than 50 mg/h of meperidine was 20% compared to 2% for women who gave themselves <50 mg/h.[11]

MAINTENANCE OF EPIDURAL LABOR ANALGESIA

Ideal Maintenance Solution

The ideal labor analgesic technique should provide constant pain relief of long duration, minimize undesirable side effects, not interfere with the progress of labor, and minimize physician involvement.[12] Local anesthetic solutions that provide complete analgesia during all of labor are associated with motor blockade and an increased incidence of instrumental vaginal delivery. Several studies have compared maintenance of analgesia with bupivacaine-only (0.25%) to solutions of low concentration bupivacaine (≤0.1%) combined with fentanyl. While the rate of cesarean delivery was not different between groups, the incidence of instrumental vaginal delivery was higher in women who received the more concentrated bupivacaine solution.[13,14] Currently, the best method of avoiding motor blockade during epidural analgesia is to combine low concentrations of local anesthetic with a lipid soluble opioid (e.g., fentanyl or sufentanil).

Methods of Delivery Labor Epidural Analgesic Solution

The method of delivering the anesthetic solution to the epidural space also influences the degree of motor block. Given the same concentration of local anesthetic, analgesia maintained by infusion compared to intermittent boluses results in greater drug utilization, a greater degree of motor blockade,[15,16] and a higher incidence of instrumental vaginal delivery.[17] However, intermittent manual bolus administration by the anesthesiologist results in more breakthrough pain, decreased patient satisfaction, and more work for the anesthesiologist. Hence, in recent years, maintenance of epidural analgesia with continuous infusions has been the norm. This requires a decrease in local anesthetic concentration in order to avoid an increased incidence of motor blockade.

Another method of administering bolus doses while minimizing breakthrough pain and anesthesiologist workload is patient controlled epidural analgesia (PCEA). Several studies have compared continuous infusions to PCEA. A meta-analysis concluded that women who had PCEA had fewer interventions by the anesthesiologist (risk difference 27% (95% CI: 18 to 36%)), used less local anesthetic, and had less motor blockade compared to women with continuous infusion epidural analgesia.[18] Ropivacaine and levobupivacaine may be associated with less motor blockade compared with equipotent doses of bupivacaine,[19–21] although this was not associated with a decreased incidence of instrumental vaginal delivery.[21]

There are conflicting data as to whether PCEA should include a background infusion. Bupivacaine consumption is higher with background infusions compared to a pure PCEA technique without a background infusion.[22] In a review of the topic, Halpern[23] concluded that a background infusion improves analgesia and may be helpful in selected parturients (e.g., nulliparas with long labors).

As discussed above, the bolus administration of epidural anesthetic solution appears to result in improved analgesia with a lower total drug dose. There may be more wide-spread distribution of anesthetic solution within the epidural space when large volumes are injected as a bolus compared to a slow infusion. Investigators have recently demonstrated that timed (automated) intermittent boluses (5 to 10 mL every 30 to 60 min) administered via a programmable pump results in improved patient satisfaction, less drug use, longer duration of analgesia, and less breakthrough pain compared to a continuous infusion of the same mass of drug per unit time.[24–27] Commercial pumps that allow easy utilization of this mode of anesthetic solution delivery are not currently available.

EPHEDRINE VS. PHENYLEPHRINE FOR TREATMENT OF NEURAXIAL ANESTHESIA-INDUCED HYPOTENSION

Ephedrine was the drug of choice for the treatment of hypotension during neuraxial anesthesia for cesarean delivery for many years. Studies in pregnant ewes suggested that ephedrine better maintained uterine blood flow compared to direct acting α-adrenergic agonists.[28] Recent evidence, however, no longer supports this practice. A number of human studies in the last 15 years have demonstrated that phenylephrine is equally effective for treating maternal hypotension. More importantly, in studies of spinal anesthesia for elective cesarean delivery, fetal acid-base status is actually improved with phenylephrine compared to ephedrine.[29–32] A meta-analysis found no differences in maternal blood pressure, although bradycardia was more likely after phenylephrine treatment.[33] Umbilical artery pH was higher after treatment with phenylephrine (weighted mean difference of 0.03; 95% CI, 0.02–0.04), however there was no difference in the number of neonates with umbilical artery pH <7.2 (RR 0.78; 95% CI, 0.16–3.92) or Apgar score <7 at 1 and 5 min.

Cooper et al.[34] compared phenylephrine, ephedrine, and phenylephrine combined with ephedrine for the treatment of hypotension after spinal anesthesia. The incidence of fetal acidosis (pH <7.2) was higher in the ephedrine group (22%) compared with the combined

phenylephrine/ephedrine group (2%); however, the incidence of nausea or vomiting was higher in the two groups that received ephedrine compared to phenylephrine alone.

Traditionally, anesthesiologists have maintained maternal blood pressure within 20% of baseline pressure. However, Ngan Kee and colleagues[35] demonstrated that umbilical artery pH is higher, and the incidence of nausea and vomiting is lower, if maternal blood pressure is maintained at 100% baseline compared to 80% baseline. Large amounts of phenylephrine are required to maintain blood pressure at baseline: (median (IQR) infusion dose before delivery 1260 μg [1010–1640 μg]).[35]

The adverse effect of ephedrine compared to phenylephrine on fetal pH is likely a direct effect of ephedrine on the fetus (increased fetal metabolic activity).[36] It is unlikely that this has any adverse effect on the healthy fetus. It is unclear whether there is an adverse effect on fetuses with decreased reserve (e.g., intrauterine growth restriction, non-reassuring fetal status during labor). It is clear that maintaining maternal blood pressure close to baseline decreases the incidence of fetal acidosis and maternal nausea and vomiting. Ephedrine has a longer duration of action than phenylephrine, and a chronotropic effect; whereas the short duration of action of phenylephrine makes it more practical to administer as an infusion. Many anesthesiologists are currently using a combination of phenylephrine and ephedrine in order to reduce the dose of both drugs, thus decreasing the likelihood of both fetal acidosis and maternal bradycardia.

CRYSTALLOID AND COLLOID ADMINISTRATION TO PREVENT HYPOTENSION DURING SPINAL ANESTHESIA

Factors associated with an increased risk for hypotension after spinal anesthesia include dose of local anesthesia (and maximum cephalad extent of blockade), low baseline blood pressure, high interspinous level of dural puncture, lack of labor (e.g., elective procedure), and increased sympathetic tone as assessed by heart rate variability indices.[37] Traditional preloading with crystalloid prior to the induction of spinal or epidural anesthesia does not significantly decrease the incidence of hypotension. In the presence of euvolemia, crystalloid solution is rapidly redistribution from the intravascular to interstitial space.[38] This may explain the ineffectiveness of preload (administered *prior* to the initiation of anesthesia, when the patient is euvolemic) in preventing hypotension. Dyer and colleagues[39] hypothesized that crystalloid administration may be more effective when administered immediately following the initiation of spinal anesthesia (termed co-load), during the development of relative hypovolemia. Indeed, the incidence of hypotension was lower and need for ephedrine less, in a group of parturients randomized to co-load (20 mL/kg) compared to a preload 20 min prior to induction.

Several groups of investigators have compared crystalloid preload to colloid (starch) preload and found that the incidence of hypotension after induction of spinal anesthesia is lower after colloid preload.[40–42] However, colloid is expensive, and some patients may have an allergic reaction. Whether routine colloid administration to all healthy women undergoing spinal anesthesia will contribute to improved outcomes is questionable.

Ngan Kee[43] demonstrated that the combination of crystalloid co-load with a prophylactic phenylephrine infusion decreased the incidence of hypotension to 1.9% (95% CI 0.3–9.9%) compared to a group who received minimal fluids with phenylephrine (28.3% (95% CI 18.0 to 41.6%)).

Taken together, these studies suggest that crystalloid be administered rapidly at the time of induction of spinal anesthesia, and the use of colloid should be considered in women considered at high risk of hypotension. Phenylephrine is no longer contraindicated for the treatment of hypotension and may be the drug of choice.

SPINAL VS. EPIDURAL ANESTHESIA FOR SEVERE PREECLAMPSIA

Traditionally, spinal anesthesia has been avoided in parturients with severe preeclampsia as it was thought that rapid onset of sympathectomy would increase the risk of hypotension in these volume-contracted women. However, in both an observational[44] and RCT,[45] there was no difference in the incidence or degree of hypotension, or in neonatal outcome, in women who received epidural compared to spinal anesthesia. Aya et al.[46] observed that women with severe preeclampsia actually had less hypotension after spinal anesthesia compared to healthy controls. The uterine artery pulsatility index does not change after the induction of spinal anesthesia.[47] Finally, Dyer and colleagues demonstrated that general compared to spinal anesthesia for urgent cesarean delivery in severely preeclamptic parturients resulted in better hemodynamic stability and better 1-min Apgar scores.[48]

Therefore, given these data, it is appropriate to induce spinal anesthesia for urgent (or elective) cesarean delivery in women with severe preeclampsia.

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The Anesthesiologist's Role in Perioperative Lung Protection

Peter Slinger, MD, FRCPC

Potential lung injuries which can occur in the perioperative period and may be influenced by anesthetic management include atelectasis, pneumonia, broncho-pleural fistula, bronchospasm and acute lung injury. Anesthesiologists deal with patients who present with both injured and non-injured lungs in the perioperative period. Non-injured lungs need to be protected from multiple factors in the perioperative period. Injured lungs need to be protected from the Anesthesiologist. This review will look at the relevant issues in both situations.

PATIENTS WITH NONINJURED LUNGS

Management of Patients with Healthy Lungs

Traditionally, anesthesiologists have been taught to ventilate patients in the operative and postoperative periods with relatively large tidal volumes. Volumes as large as 15 mL/kg ideal body weight have been suggested to avoid intraoperative atelectasis.[1] This far exceeds the normal spontaneous tidal volumes (6 mL/kg) common to most mammals.[2] Recently, it has become obvious that these nonphysiologic large tidal volumes can cause a degree of subclinical injury in healthy lungs. Gajic at al.[3] reported that 25% of patients without lung injury ventilated in an ICU setting for 2 days or longer developed acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). The main risk factors associated with the development of lung injury were the use of large tidal volumes, restrictive lung disease, and transfusion of blood products. In a prospective study, the same group have found that tidal volumes >700 mL and peak airway pressures > 30 cm H_2O were independently associated with the development of ARDS.[4] In an intraoperative study of patients having esophageal surgery Michelet et al.[5] compared the use of tidal volumes of 9 mL/kg without positive end-expiratory pressure (PEEP) during two- and one-lung ventilation versus 9 mL/kg during two-lung ventilation and 5 mL/kg during one-lung ventilation with PEEP 5 cm H_2O throughout. They found significantly lower serum makers of inflammation (cytokines IL-1β, -6 and -8) in the lower tidal volume plus PEEP group (see Fig. 1). The study did not find any major difference in postoperative outcome between the two groups, however it was not powered to do this. The study did demonstrate better oxygenation in the lower tidal volume group during and immediately after one-lung ventilation (see Fig. 2) but not after 18 h. In a study of major abdominal surgery patients ventilated for >5 h, Choi et al.[6] compared the use of 12 mL/kg tidal volumes without PEEP versus 6 mL/kg plus PEEP 10 cm H_2O. Bronchiolar lavages were performed before and after 5 h of mechanical ventilation. Lavage fluid from the high tidal volume group showed a pattern of leakage of plasma into the alveoli with increased levels of thrombin-antithrombin complexes (see Fig. 3), soluble tissue factor and factor VIIa. This is the hallmark of alveolar lung injury. A clear pattern seems to be appearing from the clinical research that, even in patients with no lung disease, the use of nonphysiologic patterns of ventilation with large tidal volumes and without PEEP causes a degree of systemic inflammation and lung injury. The severity of this injury seems to be directly related to the duration of mechanical ventilation.

Patients with Chronic Obstructive Pulmonary Disease (COPD)

COPD incorporates three disorders: emphysema, peripheral airways disease, and chronic bronchitis. COPD patients are at an increased risk for lung injury in the perioperative period. Recent advances in the understanding of COPD that are relevant to anesthetic management and perioperative lung injury include:

Dynamic hyperinflation. Emphysema is, almost exclusively, an expiratory disease unlike asthma or chronic bronchitis, which have both inspiratory and expiratory components. As a result, it is easy to get gas into the emphysema patient's lungs during positive pressure ventilation but extremely difficult to get the gas out due to intrinsic PEEP (auto-PEEP). This intrathoracic gas-trapping is referred to as "Dynamic Hyperinflation." .[7] Even seemingly low levels of positive airway pressure in these patients, such as those generated by bag-mask ventilation during induction of anesthesia, can lead to severe hyperinflation with secondary impairment of cardiac venous return leading to hypotension and even cardiac arrest. This hemodynamic effect is exacerbated in the presence of decreased intravascular volume and vasodilating anesthetic agents. Dynamic Hyperinflation is the cause of some of the instances of the "Lazarus Syndrome," in

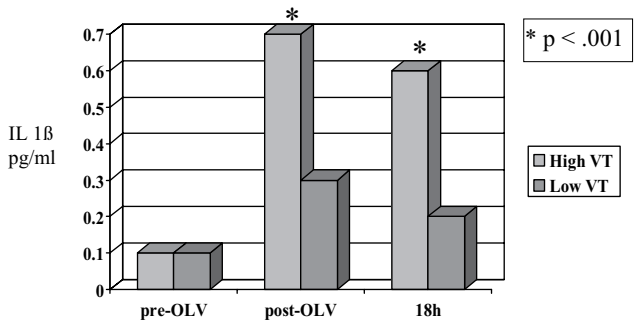

Figure 1. Serum levels of inflammatory cytokine IL 1-β before and after periods of one-lung ventilation (OLV) in patients having esophagectomies. Patients' lungs were ventilated with either a large tidal volume (9 mL/kg) or a small tidal volume (5 mL/kg) plus PEEP (5 cm H_2O) during OLV. Based on data from Michelet et al.[5]

which patients with COPD who have had a cardiorespiratory arrest and have been pronounced dead after failed resuscitation have spontaneously recovered once resuscitation is stopped.[8]

Anesthesiologists must be very aware of the possibility of dynamic hyperinflation whenever general anesthesia is induced in a patient with emphysema. The primary methods to avoid hemodynamic instability in these patients are ventilatory management: thorough preoxygenation prior to induction, then the use of small tidal volumes, slow respiratory rates and long expiratory times and tolerance of hypercarbia until the patient recovers from the vasodepressant effects of induction drugs. Also important for these patients are: large-bore IV access, vasopressors, and inotropes immediately available and IV preloading with colloids or crystalloids.

An extremely difficult differential diagnosis arises when one of these patients "crashes" during positive pressure ventilation. The diagnostic dilemma is to differentiate between tension pneumothorax and dynamic hyperinflation. The choice is not always obvious and the definitive treatments are very different. Unilateral changes in chest auscultation, tracheal deviation and the presence of known bullae favor pneumothorax and the need for decompression. In the absence of these clues, it is best to stop ventilation and let the patient breath out passively to atmosphere while beginning pharmacologic resuscitation. With hyperinflation there will be a gradual return of circulation, but it is not immediate. If there is no improvement after 1 minute of apnea, the assumption should be pnemothorax and chest drains should be placed.

Bullae. Many patients with moderate or severe COPD develop cystic air spaces in the lung parenchyma known as bullae. These bullae will often be asymptomatic unless they occupy more than 50% of the hemithorax, in which case the patient will present with findings of restrictive respiratory disease in addition to their obstructive disease. Previously, it was thought that bullae represented positive pressure areas within the lung that compressed surrounding lung tissue. It is now appreciated that a bulla is actually a localized area of loss of structural support tissue in the lung with elastic recoil of surrounding parenchyma. The pressure in a bulla is actually the mean pressure in the surrounding alveoli averaged over the respiratory cycle. This means that during normal spontaneous ventilation the intrabulla pressure is actually slightly negative in comparison to the surrounding parenchyma.[9] However, whenever positive-pressure ventilation is used the pressure in a bulla will become positive in relation to the adjacent lung tissue and the bulla will expand with the attendant risk of rupture, tension pnuemothorax and bronchopleural fistula. Positive-pressure ventilation can be used safely in patients with bullae provided the airway pressures are kept low and there is adequate expertise and equipment immediately available to insert a chest drain and obtain lung isolation if necessary.

Respiratory drive. Many COPD patients have an elevated $Paco_2$ at rest. Among moderate and severe COPD patients it is not possible to predict from history or physical examination which patients are "CO_2-retainers."[10] Preoperative arterial blood a gases are required to set goals for intra- and postoperative ventilation. This CO_2-retention seems to be primarily related to an inability to maintain the increased work of respiration and not due to an alteration of respiratory control mechanisms.[11] The $Paco_2$ rises in these patients when supplemental oxygen is administered not due to a decrease of minute ventilation,[12] but because a high FiO_2 causes a relative increase in alveolar dead space by the redistribution of lung perfusion and also due to the Haldane effect.[13] However, supplemental oxygen must be administered to these patients postoperatively to prevent hypoxemia. The attendant rise in $Paco_2$ should be anticipated and monitored. Hypercarbia is usually well tolerated in the absence of intracranial pathology and if the vasodepressant effects of acidosis can be managed.[14] In addition to arterial blood gas monitoring, the best monitor of dangerous hypercarbia is the patient's level of consciousness. At levels >80–100 mm|Hg $Paco_2$ carbon dioxide begins to have a sedative and anesthetic effect.

Nocturnal hypoxemia. COPD patients desaturate more frequently and severely than normal patients during sleep. This is related to the shallow rapid pattern of ventilation which occurs in all patients during REM sleep.[15] 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 (RV) dysfunction. Right ventricular dysfunction occurs in up to 50% of COPD patients.[16] The dysfunctional RV is poorly tolerant of sudden increases in afterload such as the change from spontaneous to controlled ventilation or large pulmonary resections.[17]

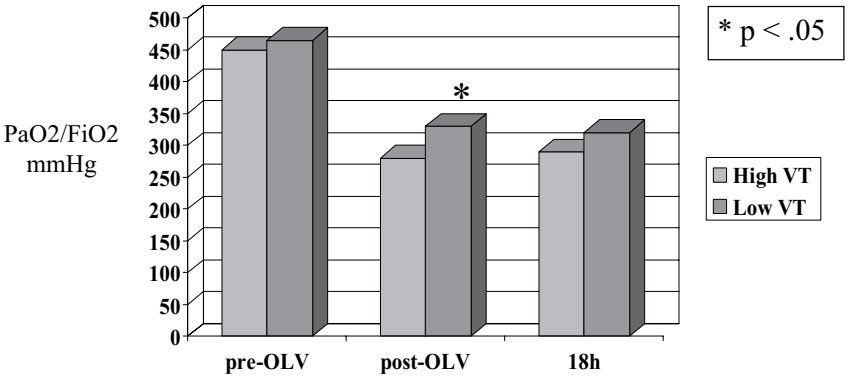

Figure 2. Ratio of arterial oxygen tension to inspired oxygen concentration (PAo_2/FiO_2) in patients ventilated with either a large tidal volume (9 mL/kg) or a small tidal volume (5 mL/kg) plus PEEP (5 cm H_2O) during OLV. Based on data from Michelet et al.[5]

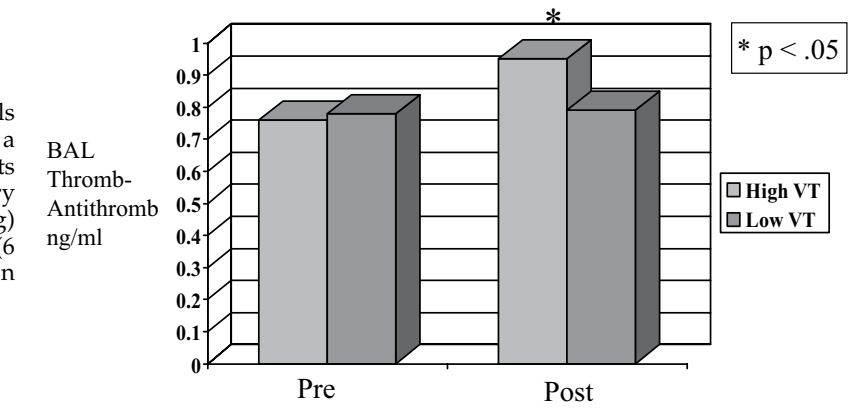

Figure 3. Bronchoalveolar lavage (BAL) levels of thrombin-antithrombin complexes as a marker of lung epithelial injury in patients ventilated for >5 h during abdominal surgery with either a large tidal volume (12 mL/kg) without PEEP vs a small tidal volume (6 mL/kg) with PEEP (10 cm H_2O). Based on data from Choi et al.[6]

Perioperative Therapy of COPD to Decrease Lung Injury

Physiotherapy. It has been clearly shown that patients with COPD have fewer postoperative pulmonary complications when a perioperative program of intensive chest physiotherapy is initiated preoperatively.[18] Even in the most severe COPD patient it is possible to improve exercise tolerance with a physiotherapy program.[19] Little improvement is seen before 1 month. Among COPD patients, those with excessive sputum benefit the most from chest physiotherapy.[20]

Smoking cessation. A preoperative smoking cessation program can significantly decrease the incidence of respiratory complications (4–8 weeks abstinence), wound complications (4 weeks abstinence) and intraoperative myocardial ischemia (48 h abstinence).[21]

Bronchodilation. Bronchoconstriction is assessed by history, physical examination, and evaluation of pulmonary function response to bronchodilators. All asthma/COPD patients should receive maximal bronchodilator therapy as guided by their symptoms. In a patient who is poorly controlled on sympathomimetic and anticholinergic bronchodilators, a trial of corticosteroids may be beneficial.[22] It is not clear if corticosteroids are as beneficial in COPD as they are in asthma.

Are pulmonary function tests needed? Yes. PFTs are not useful as screening tools for all patients, but flow-rates are valuable to assess symptomatic patients, to confirm the diagnosis, and to assess the adequacy of therapy.

Is referral to a chest physician indicated? The anesthesiologist will have to decide if the patient with reactive airways disease is adequately managed preoperatively, i.e., functionally at his or her usual level of exercise tolerance and with flow-rates >80% of stable baseline. If preoperative management of bronchospasm is inadequate or if there is any evidence of current respiratory infection, the patient should be referred to a chest or family physician for therapy preoperatively.

With advances in anesthetic management the incidence of life-threatening intraoperative bronchospasm has become very low.[23] However, the anesthesiologist must always respect the management principles for patients with reactive airways: preoperative optimization of bronchodilation, minimal (or no) instrumentation of the airways, instrument the airways when necessary only after appropriate depth of anesthesia with a bronchodilating anesthetic (propofol, ketamine, sevoflurane), and maintenance of anesthesia with a bronchodilating anesthetic and appropriate warming and humidification of inspired gases.[24] In patients with bronchial hyper-reactivity (FEV1 <70% and >10% increase with bronchodilator) on regular bronchodilator therapy, postintubation wheezing can be significantly reduced by addition of a 5-day preoperative course of corticosteroids (methylprednisolone 40 mg/day p.o.).[25] Inhaled corticosteroids may also be useful in this regard.

Perioperative Surgical Environment Factors

There are multiple factors in the surgical environment that can contribute to lung injury. One of the most obvious is the surgical approach. If major body

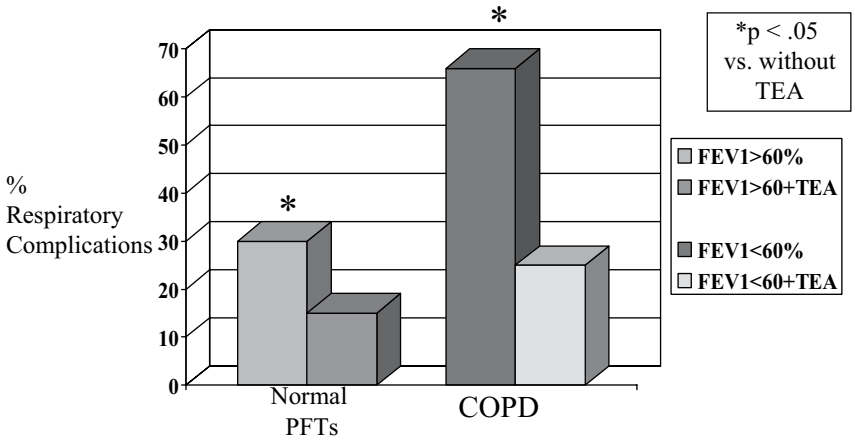

Figure 4. Percent of patients experiencing postoperative respiratory complications in a retrospective study following thoracic surgery for lung cancer. The benefits of thoracic epidural analgesia were more marked in patients with chronic obstructive pulmonary disease (COPD) than in patients with normal preoperative pulmonary function tests (PFTs). Based on data from Licker et al.[39]

cavity procedures can be done with a minimally-invasive versus open technique, the decrease in respiratory complications is well documented.[26]

Atelectasis is a frequent postoperative complication of open surgical procedures. Atelectasis occurs intraoperatively as part of essentially any general anesthetic.[27] Anesthesiologists are aware of this, and techniques to avoid it with air-oxygen mixtures, PEEP, and recruitment maneuvers are used frequently.[28] However, anesthesiologists are often not aware that atelectasis is a pathological state, and if it persists in the postoperative period leads to increased capillary permeability and an inflammatory response with subsequent lung injury.[29] Both retrospective[30] and prospective[31] studies have consistently 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 (see Fig. 4). It has also been recently demonstrated that aggressive physiotherapy with CPAP in the postoperative period in patients who develop early desaturation after major abdominal surgery leads to lower rates of major respiratory complications.[32]

PATIENTS WITH INJURED LUNGS

There are situations when the anesthesiologist appreciates that a patient presenting for surgery may have a lung injury (trauma/ARDS, lung transplantation, etc.), however there are many more cases where the lung injury is subclinical and underappreciated in the perioperative period (cardiopulmonary bypass, large pulmonary resections[33]). Acute lung injury following pulmonary resection has been described since the beginning of one-lung ventilation (OLV) for thoracic surgery. The most publicized report is a compilation of 10 cases following pneumonectomy published in 1984[34] which focused on the role of IV overhydration as a cause of post-pneumonectomy pulmonary edema. Subsequently, there have been several reviews of this topic identifying a variety of other potentially causative factors for ALI such as the administration of fresh frozen plasma, mediastinal lymphatic damage, inflammation, and oxygen toxicity.[35] The most thorough study to date[36] is a retrospective survey of 806 pneumonectomies that found 21 cases (2.5%) of post-pneumonectomy pulmonary edema, one of the lowest incidences reported of this complication. There were no differences in perioperative fluid balance between post-pneumonectomy ALI cases (positive fluid balance at 24 h: 10 mL/kg) versus matched pneumonectomy controls (13 mL/kg). These authors used rigorous fluid restriction compared to other reports[37] (e.g., 24 h positive balance: 21 ± 9 mL/kg), suggesting that limiting intraoperative fluids might decrease but not eliminate ALI. Further reports demonstrate improved survival from post-pneumonectomy pulmonary edema is likely due to improved postoperative management of established cases.[38]

ALI after pulmonary resection has been found to have a bimodal distribution of onset. Late cases (10/37, 27%) presented 3–10 days postoperatively and were secondary to obvious causes such as bronchopneumonia, aspiration, etc. "Primary" ALI (27/37, 73% of cases) presented on postoperative days 0–3. Four factors were independent significant predictors of primary ALI: high intraoperative ventilation pressures, excessive IV volume replacement, pneumonectomy, and preoperative alcohol abuse.[39] The known facts about ALI following lung surgery thus include: an incidence of 2–4% following pneumonectomy; greater frequency in right versus left pneumonectomies; symptomatic onset 1–3 days after surgery; high associated mortality (25–50%); and resistance to standard therapies. While ALI occurs following lesser pulmonary resections such as lobectomy, it has a much lower mortality rate. Of interest, in 8 of 9 cases who developed unilateral ALI following lobectomy, the ALI was in the nonoperated (i.e., ventilated) lung.[40]

While there is some association between postoperative ALI and fluid overload, the finding of low/normal pulmonary artery wedge pressures and high-protein edema fluid in affected patients suggests a role

of endothelial damage (low-pressure pulmonary edema). Postoperative increases in lung capillary permeability of the nonoperated lung occur after pneumonectomy but not lobectomy.[41]This capillary-leak injury may be due to an inflammatory cascade affecting even the nonoperative lung that is triggered by lung resection and is proportional to the amount of lung tissue resected.[42,43] Free oxygen radical generation in lung cancer patients is related to the duration of OLV.[44]Nonetheless, there is no single mechanism that can fully explain ALI after lung resection and its etiology is likely multifactorial. A unifying hypothesis is that post-pneumonectomy pulmonary edema is one end of a spectrum of ALI that occurs during all lung resections. The more extensive the resection the more likely there is to be a postoperative injury. The increased dissection and trauma associated with extrapleural pneumonectomy places these patients at high risk to develop postoperative ALI.[45]

Understanding that lung endothelial injury occurs after lung resection supports management strategies similar to other conditions associated with ALI and ARDS. As a general principle, it seems that the lung is least injured when a pattern of ventilation as close as possible to normal spontaneous ventilation can be followed: FiO_2 as low as acceptable, variable tidal volumes,[46]beginning inspiration at FRC, and avoiding atelectasis with frequent recruitment maneuvers.[47] Studies in ARDS demonstrate that ALI is exacerbated by the use of large tidal volumes and that lung-protective ventilation strategies with low tidal volumes and PEEP are less injurious. The most important factor in the etiology of ventilator-induced lung injury is the end-inspiratory lung volume.[48] Many patients, particularly those with emphysema, develop auto-PEEP during one-lung ventilation,[49] thus beginning inspiration at a lung volume above functional residual capacity. It is conceivable that routine use of large tidal volumes (10–12 mL/kg) during OLV in such patients produces end-inspiratory lung volumes close to levels that contribute to ALI.

Changes in respiratory function during OLV in the lateral position with an open nondependent hemithorax are complex. Initial studies of the application of PEEP during OLV suggested that it led to a deterioration of arterial oxygenation.[50] It is now appreciated that the effects of applied PEEP during OLV depend on the lung mechanics of the individual patient. Most patients with COPD develop auto-PEEP during OLV and thus adding external PEEP leads to hyperinflation and increased shunt51 (see Fig. 5). However, patients with normal lung parenchyma or those with restrictive lung diseases tend to fall below their FRC at end-expiration during OLV (see Fig. 6) and benefit from applied external PEEP.[52] Intraoperative atelectasis may contribute to injury in the dependent lung. It is now appreciated that atelectasis is a preinflammatory state predisposing to injury both in the atelectatic

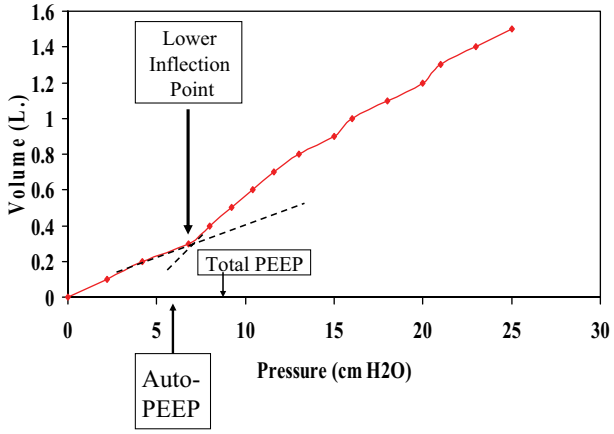

Figure 5. The inspiratory compliance curve (lung volume vs airway pressure) during one-lung ventilation as the lung is slowly inflated by 100 mL increments in a patient with mild COPD. The lower inflection point of the curve [thought to represent functional residual capacity (FRC)] is at 7 cm H_2O. During OLV this patient developed an intrinsic PEEP (measured by end-expiratory airway occlusion plateau pressure "Auto-PEEP") of 6 cm H_2O. The addition of 5 cm PEEP through the ventilator resulted in a total PEEP in the circuit of 9 cm. The addition of PEEP in this patient raised the end-expiratory lung volume above FRC, thus raising pulmonary vascular resistance in the ventilated lung and caused a deterioration in oxygenation. Based on data from Slinger et al.[51]

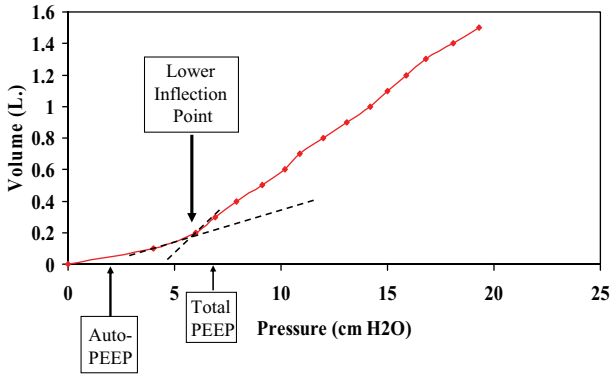

Figure 6. The inspiratory compliance curve during OLV in a patient with normal pulmonary function. The lower inflection point of the curve is at 6 cm H_2O. During OLV this patient developed an intrinsic PEEP of 2 cm H_2O. The addition of 5 cm PEEP through the ventilator resulted in a total PEEP in the circuit of 7 cm. The addition of PEEP in this patient raised the end-expiratory lung volume to FRC thus decreasing pulmonary vascular resistance in the ventilated lung and caused an improvement in oxygenation. Based on data from Slinger et al.[51]

portion of the lung and in ventilated regions in the same lung, which become hyperinflated.[53]

There is evidence that when an element of lung injury is added to large tidal volume ventilation during OLV, this contributes to ALI. In a rabbit model of OLV during isolated perfusion, large tidal-volume (8 mL/kg) ventilation produced a picture of ALI absent in animals randomized to a lung-protective ventilation pattern (4 mL/kg plus PEEP).[54] In a sheep-pneumonectomy model, the use of large tidal volume

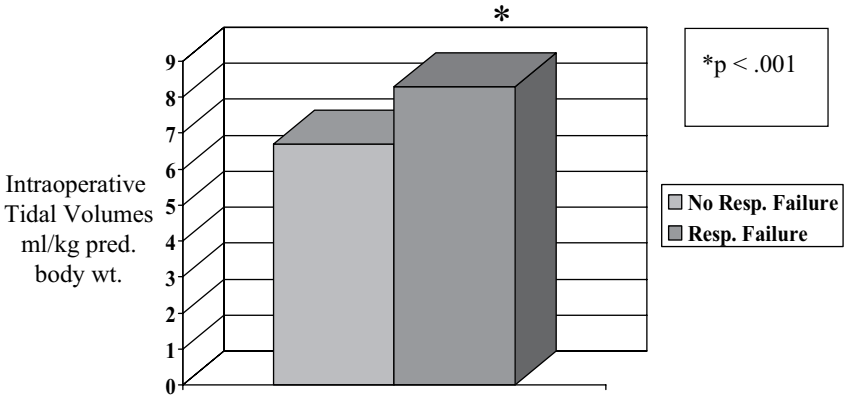

Figure 7. Retrospective analysis of the tidal volumes used during pneumonectomy in patients who developed postoperative respiratory failure vs patients who did not develop respiratory failure. The respiratory failure patients received larger tidal volumes. Based on data from Fernandez-Perez et al.[58]

ventilation (12 mL/kg) was associated with a significant increase in postoperative lung water not seen in animals ventilated with smaller tidal volumes or controls.[55] Another consideration is management of patients who have received preoperative chemotherapy with agents such as cisplatinum and gemcitabine that may affect respiratory function and may increase the risk of postoperative respiratory complications including ALI in some patients.[56] Large pulmonary resections (pneumonectomy or bilobectomy) should be considered to be associated with some degree of ALI. Acute lung injury, diagnosed radiographically, was reported in 42% of pneumonectomy patients who had been ventilated with peak airway pressures >40 cm H_2O.[57] A recent retrospective study found that post-pneumonectomy respiratory failure was associated with the use of higher intraoperative tidal volumes (8.3 mL/kg vs 6.7 mL/kg in pneumonectomy patients who did not develop respiratory failure) (see Fig. 7).[58]

Since it is not always possible to predict which patient scheduled for a lobectomy may require a pneumonectomy for complete tumor resection, the routine use of several lung protective strategies during OLV seem logical. Overinflation of the nonoperated lung should be avoided using lung-protective ventilation (5–6 mL/kg) adding PEEP to those patients without auto-PEEP and limiting plateau and peak inspiratory pressures to <25 cm H_2O and <35 cm H_2O, respectively. Minimizing pulmonary capillary pressures by avoiding overhydration for patients undergoing pneumonectomy is reasonable, while acknowledging that not all increases in pulmonary artery pressures perioperatively are due to intravascular volume replacement. Other factors such as hypercarbia, hypoxemia, and pain can all increase pulmonary pressures and must be treated. Finally, it must be appreciated that not all hyperinflation of the residual lung occurs in the operating room. Overexpansion of the remaining lung after a pneumonectomy may occur postoperatively either with or without a chest drain in place. The use of a balanced chest drainage system to keep the mediastinum in a neutral position and avoid hyperinflation of the residual lung following a pneumonectomy has been suggested to contribute to a marked decline in this complication in some centers.[59]

Cardiopulmonary bypass causes a subclinical lung injury that can be aggravated by injurious ventilation patterns. Zupancich et al.[60] compared the use of nonprotective high tidal volumes (10–12 mL/kg) plus low PEEP (2–3 cm H_2O) versus lung protective low tidal volumes (8 mL/kg) plus high PEEP (10 cm H_2O) in patients ventilated for 6 h following cardiopulmonary bypass for coronary artery bypass surgery. Serum and bronchiolar lavage levels of the inflammatory cytokines IL-6 and IL–8 were significantly increased at 6 h only in the nonprotective ventilation group (see Fig. 8).

TRANSFUSION RELATED ACUTE LUNG INJURY (TRALI)

Over the past 20 years, acute lung injury secondary to transfusion of blood products has become recognized as a distinct clinical entity. It crosses the boundaries between patients with and without lung injury

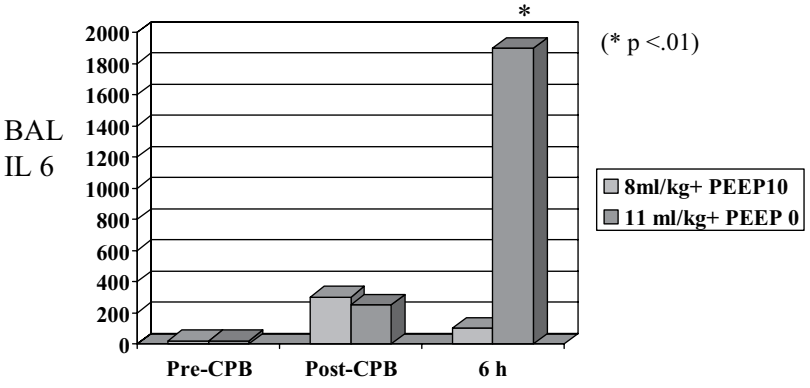

Figure 8. Bronchoalveolar lavage (BAL) levels in patients ventilated for 6 h after cardiopulmonary bypass (CPB) for coronary artery bypass surgery. Patients ventilated with larger tidal volumes (11 mL/kg) without PEEP had increased levels of the inflammatory cytokine IL-6 vs patients ventilated with smaller tidal volumes (8 mL/kg) with PEEP 10 cm H_2O. Based on data from Zupancich et al.[60]

because it can cause injury to healthy lungs or it can exacerbate incipient lung injury.[61] The etiology of TRALI is primarily due anti-white blood cell antibodies in the transfused serum. These antibodies can be to either human leukocyte antigens (HLAs) or human neutrophil antigens (HNAs). HNA antibodies can bind to and trigger neutrophils and leukocytes in the recipient. HLAs are more widespread and these antibodies can react with white blood cells and/or the pulmonary endothelium of the recipient. Neutrophils normally are flexible and are deformed as they pass through the lung, since the diameter of 50% of the pulmonary capillaries is smaller than the neutrophils. Priming of the neutrophils by sepsis, inflammation or immune triggering (as in the case of TRALI) stiffens the neutrophils which then become sequestered in the pulmonary capillary bed. This process can be aggravated by any physical injury to the endothelium which causes the release of intercellular adhesion molecules which then cause transendothelial migration of the sequestered neutrophils into the interstitium of the lung parenchyma, beginning the process of injury. The process seems to be a two-hit phenomenon usually requiring both a degree of lung injury and priming of the circulating neutrophils. Although TRALI can occur unrelated to surgery, a disproportionate number of cases occur in the perioperative period.[62]Some partially preventative measures are open to blood bankers such as the use of washed red cells, leukocyte depleted red cells, and avoiding plasma donations from multiparous females. However the major burden of prevention falls on the anesthesiologist to avoid unnecessary transfusion of blood products and to decrease the potential for perioperative mechanical lung injury.

PREVENTION AND THERAPY FOR THERAPY FOR ACUTE LUNG INJURY

Apart from mechanical ventilation strategies, a number of other therapies have been suggested to prevent or treat acute lung injury. Early reports comparing the use of volatile vs. IV anesthetics[63] have shown mixed results with respect to the ability of anesthetic agents to affect immune responses and lung endothelial injury.[64] Randomized placebo-controlled trials of several different therapies including surfactant, prone positioning, inhaled nitric oxide and anti-inflammatories have not shown significant clinical benefits in patients with established acute lung injury.[65] β-adrenergic agents are currently generating much interest as a potential treatment for acute lung injury.[66] β-agonists increase the rate of alveolar fluid clearance by increasing cellular cyclic adenosine monophophate (cAMP) in the epithelium, also β-agonists have anti-inflammatory properties. In a randomized placebo-controlled study in 40 patients with acute lung injury, Perkins et al. [67] found that the use of IV salbutamol decreased lung water and plateau airway pressure, although there were no significant differences in outcome. A randomized study of inhaled salmeterol has shown that it can reduce the incidence of high altitude pulmonary edema in subjects at risk.[68] Although studies of extracorporeal membrane oxygenation have not shown survival benefits in adults, a pumpless extracorporeal membrane ventilator may be of some benefit.[69]

SUMMARY

There are several evidence-based strategies that can reduce the incidence of perioperative lung injury in patients with noninjured lungs; these include avoidance of bronchospasm, discontinuation of smoking, physiotherapy, and aggressive treatment of atelectasis. The use of epidural analgesia has been demonstrated to reduce respiratory complications in patients with COPD having major surgery. The use of lung-protective mechanical ventilation strategies intraoperatively has not been proven to improve outcomes in this group. However, evidence is accumulating that traditional large-volume tidal volume ventilation without PEEP cases a subclinical lung injury in proportion to the duration of mechanical ventilation in patients with healthy lungs.

There are more patients than commonly appreciated who are at increased risk for acute lung injury during surgery; these include patients with large pulmonary resections and those exposed to cardiopulmonary bypass. Given the low risks, lung protective ventilation strategies, including using low-tidal volumes and the selective use of PEEP, would seem to be a logical choice for ventilation management for these patients in the current era of a low frequency of hypoxemia and continuous arterial oxygen saturation monitoring.

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