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Morbid Obesity, Obesity Hypoventilation Syndrome, Overlap Syndrome: Birds of the Same Feather?

Raviraj Raveendran, MBBS, FANZCA
Specialist Anesthesiologist, West Coast District Health Board, Greymouth, New Zealand

Frances Chung, MBBS, FRCPC
Professor, Department of Anesthesia, Toronto Western Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada

INTRODUCTION

Obesity is a growing problem in both developed and developing countries and a major cause of death and disability.[1] The incidence of sleep disorder breathing is increasing proportional to the obesity incidence. Obstructive sleep apnea (OSA) is the most common sleep disorder breathing, characterised by recurrent episodes of upper airway obstruction with recurrent cycles of desaturation. Morbid obesity is an important risk factor for other sleep disorder breathing conditions like obesity hypoventilation syndrome (OHS) and overlap syndrome.

Daytime hypercapnia is the differentiating feature of OHS and overlap syndrome that separates it from simple obesity and OSA. The overlap syndrome is the term used to describe the association of chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA).[2] OHS and overlap syndrome are associated with higher morbidity and mortality than OSA alone. A recent cohort showed that 3-year mortality of OHS patients are worse than breast and colon cancer patients.[3] The awareness about OHS and overlap syndrome are very minimal and the literature related to the perioperative outcomes are limited.[4,5] Since most of the patients with OHV and overlap syndrome are not diagnosed and the morbidity is higher than patients with OSA, this poses a great challenge to the perioperative team. In this review we discuss the updated evidence on OSA, OHS and overlap syndrome in morbidly obese patients.

Definitions

Obesity is defined as a Body Mass Index (BMI) > 30 kg/m^2, morbid obesity defined as > 35 kg/m^2, super morbid obesity > 50 kg/m^2 and ultra-obesity > 70 kg/m^2. The severity of OSA is determined by Apnea Hypopnea Index (AHI), which is defined as the average number of abnormal breathing events per hour of sleep. Apnea refers to cessation of airflow for 10s, while hypopnea occurs with reduced airflow with desaturation ≥4%.[6] The American Academy of Sleep Medicine (AASM) diagnostic criteria for OSA requires either an AHI ≥15, or AHI ≥5 with symptoms, such as daytime sleepiness, loud snoring, or observed obstruction during sleep.[7] Severity of OSA is mild for AHI ≥5 to 15, moderate for AHI 15 to 30, and severe for AHI >30 events/hr.[7] OHS is defined by a resting daytime $PaCO_2$ of more than 45 mmHg, a BMI more than 30 kg/m^2, absence of an alternative cause for alveolar hypoventilation, and, although not part of the diagnostic criteria, is associated with worsened nocturnal hypercapnia, nocturnal hypoxemia, and obstructive sleep apnea (OSA). Other than OHS, the other sleep related hypoventilation disorders described by the International Classification of Sleep Disorders are congenital central alveolar hypoventilation syndrome, late-onset central hypoventilation with hypothalamic dysfunction, idiopathic central alveolar hypoventilation, sleep related hypoventilation due to a medication or substance and sleep related hypoventilation due to a medical disorder.[8] Overlap syndrome is coexistent of OSA and COPD rather than a pathophysiological link.

Epidemiology

The prevalence of obesity among adults in the United States is 34.9 % and the prevalence of Class III obesity (BMI ≥ 40 kg/m^2) was 6.3 %.[9] The prevalence of OSA among the general population aged 30 to 70 years is 5% in women and 14% in men[10] and is 78% in morbidly obese patients scheduled for bariatric surgery.[11] The incidence of OHS is approximately 0.15–0.6% of the general population.[12] OHS is more commonly in sleep disorders clinics, with prevalence of 9 to 20% of the referred obese patients.[12,13] Various epidemiologic studies confirm similar rates of OHS among referred patients: 10–17% in Europe,[14] 12.3% of obese patients with OSA in Japan[13], 8.5% of all referred patients, and 21% of referred patients with BMI more than 40 kg/m^2 in Saudi Arabia[15], and as high as 51% prevalence in a population of obese patients with chronic hypoxemia in Canada.[16]

In general the OHS incidence increases with the severity of obesity. Regarding gender difference, in contrast with OSA, recent study from the Saudi population showed a higher incidence of OHS in women (15.4%) versus men (4.5%).[15] The increased prevalence of OHS in postmenopausal women may be explained by the impact of reduction in progesterone on hormone-related respiratory drive.[17]

Regarding the overlap syndrome, the actual incidence is not known. With a 10 % prevalence of COPD and 5-10% prevalence of OSA in adult population, the calculated prevalence is 0.5 to 1% of the general population over 40 years of age.[18] The incidence of daytime hypercapnia, respiratory failure and pulmonary hypertension is more in overlap syndrome than in isolated OSA and COPD.[19]

Pathophysiology of OHS

Obesity has a significant effect on the physiology of breathing. There is significant reduction in lung compliance and functional residual capacity (FRC). CO diffusing capacity is normal or increased due to increase in pulmonary blood flow. The airway resistance is also significantly higher in the obese and it is related to the reduction in lung volume rather than airway obstruction. This contributes to OSA. Subjects with simple obesity have an enhanced respiratory drive, while the respiratory drive of subjects with obesity hypoventilation syndrome is either depressed or inappropriately suppressed.[20] Patients with OHS have increased upper airway resistance in

both the sitting as well as supine position in comparison with obese individuals without hypercapnia.[21] Nearly 90% of OHS patients have concomitant OSA, roughly 10% do not have sufficient hypopneas or apneas to meet criteria for OSA. These group of patients are found to have worsening of hypoventilation during sleep, particularly REM sleep.[22] This also contribute to the increased work of breathing in OHS patients.[23] There are different hypotheses regarding the development of OHS: obesity-induced impairment in respiratory mechanics, leptin resistance, and impaired compensation for acute hypercapnia in OSA.[24,25]

Table 1: Differences between overlap syndrome and OHS

	OHS	Overlap Syndrome
Definition	Obesity (BMI > 30 kg/m2) + Day time hypercapnia (PaCO2 > 45 mmHg) ± OSA	COPD + OSA
Prevalence in the general population	0.15–0.6%	0.5 to 1%
Relationship with OSA	Pathophysiological link in 90% cases	Coexistent & no pathophysiological link
Hypercapnic ventilator response	Decreased	Normal, enhanced or decreased
Pulmonary hypertension	+ to ++	++ to +++

+: mild increase; ++ moderate increase; +++severe increase.

Respiratory Mechanics

The type of obesity plays a vital role in respiratory mechanics. A central pattern of fat distribution is predictive of the impairments in pulmonary function more than BMI. This leads to lower lung volumes and changes the elastic recoil balance between the chest wall and lung.[26] This increases the lung resistance and reduces the compliance of lung.[27] The respiratory compliance is 60% less in OHS compared to 20% less in eucapnic obese. All these causes a three fold increase in the work of breathing.[23] Hence, OHS patients maintain an increased oxygen cost of breathing (15% vs. 3% in nonobese), which may result in a relative state of respiratory muscle fatigue. The role of diaphragmatic weakness in the pathogenesis of OHS is not clear. The respiratory muscle weakness is improved by the application of positive airway pressure (PAP) therapy, which unloads the inspiratory muscles in patients with OHS.[28] A central fat deposition causes more cephalic displacement of diaphragm, which compresses the dependent lung zones and closes the small airways.

Ventilatory Response

In general obese patients have higher rate of oxygen consumption and CO_2 production. This increase in CO_2 production is compensated by an increase in minute ventilation.[29] This increase in central drive is not present in hypercapnic OHS patients due to the blunted neural response to hypercapnia.[30] This results in daytime hypercapnia in patients with OHS. In the initial stage of the disease process, hypercapnia occurs only during REM sleep and over time the buffering of raised carbon dioxide produces a secondary depression of respiratory drive and causes daytime hypercapnia.[31](Fig 1)

Neurohumoral and Leptin Resistance

Metabolic component of obesity has its effect on the pathogenesis of OHS. Leptin is a respiratory stimulant produced by adipose tissue. Elevation in leptin level is a compensatory mechanism in eucapnic obese patients. Leptin resistance is considered as a cause of hypercapnia in OHS.[32] Interestingly, leptin level is a better predictor of hypercapnia than the degree of adiposity.

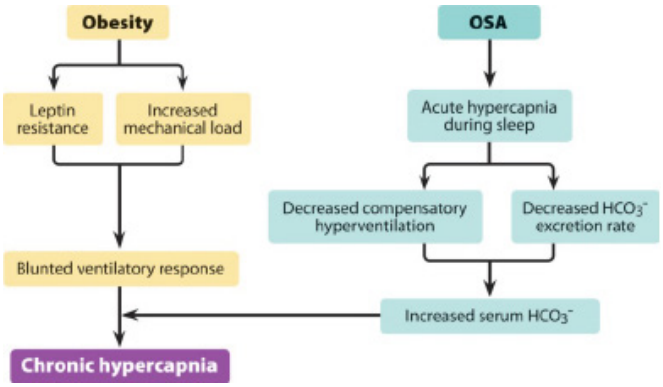

Figure: 1 Mechanisms by which obesity and OSA result in chronic hypercapnia.
Chau EH, et al. Anesthesiology 2012; 117:188-205
HCO3-_serum bicarbonate;
OSA obstructive sleep apnea.

Pathophysiology of the Overlap Syndrome

Overlap patients present with both upper and lower airway obstruction due to OSA and COPD respectively. The main factors that influence the relationship between OSA and COPD are smoking and obesity. Obesity is an important risk factor for OSA. At the same time, smoking is an important risk factor for COPD as well as OSA. Smokers have three time more chance of OSA than non-smokers.[33]

COPD patients have alveolar hypoventilation and ventilation perfusion (V/Q) mismatch and present with chronic hypoxia. However, OSA patients have a normal saturation between respiratory events. The preexisting hypoxia and ventilatory impairment of COPD is worsen by the obstructive airway during sleep in a patient with OSA. In the overlap syndrome, the flattening of the diaphragm due to COPD decreases the respiratory movement and increases the dead space ventilation which necessitates an increased accessory muscle contribution to breathing.[34] In the advanced COPD, skeletal muscle atrophy can cause further deterioriation of the contribution by the accessary muscles.[35]

COPD treatment with inhaled corticosteroids may cause local pharyngeal muscle myopathy and worsening of OSA. Also in COPD with right-heart failure, redistribution of edema fluid during supine sleep also contributes to OSA. In contrast to OHS, patients with an Overlap syndrome have a normal or even enhanced ventilator response to CO_2. Though there is no pathologic link between COPD and OSA, the combination has more severe nocturnal desaturation due

to the synergistic effect of both condtions.[36] Hypercapnia in overlap syndrome is based on the severity of COPD and OSA and it is not a mandatory criteria. Although Overlap syndrome and OHS are different conditions, they share some common clinical features. (Table 1)

Associated Comorbid Conditions

Morbid obesity is considered as an independent risk factor for various cardiovascular comorbidity. Association of sleep disorder breathing condition: OSA, OHS and overlap syndrome increases the incidence and severity of comorbidities. Though OSA is not a component of metabolic syndrome (central obesity, hypertension, hyperlipidemia and insulin resistance), there are experimental and clinical evidence to show the relationship between OSA and cardiometabolic syndrome.[37] Compared with obese patients with eucapnia, OHS patients were more likely to develop heart failure (odds ratio (OR) 9, 95% CI 2.3–35), angina pectoris (OR 9, 95% CI 1.4 –57.1) and cor pulmonale (OR 9, 95% CI 1.4 –57.1).[38] Malignant Obesity Hypoventilation Syndrome (MOHS) is defined as a patient with a BMI > 40 kg/m2 with awake hypercapnia ($PaCO_2$ > 45 mm Hg), the metabolic syndrome and multi-organ dysfunction related to obesity.[39] Nearly 75% of these patients are misdiagnosed as COPD with respiratory failure.

The Obesity Supine Death syndrome (OSDS) is a condition characterized by sudden cardiac arrest, due to severe hypoxemia with supine position in the morbidly obese patients.[40] Other than left ventricular (LV) hypertrophy with LV diastolic dysfunction and pulmonary hypertension with right ventricular (RV) overload, the direct infiltration or fat metaplasia of the heart has been reported as cardiomyopathy of obesity.[41] Nearly 61% of MOHS patients were diagnosed with non-alcoholic steatohepatitis (NASH). Obesity-related glomerulopathy, also called idiopathic focal segmental glomerulosclerosis (FSGS) is a reversible form of renal disease described in morbidly obese patients.[42] In one study, the incidence of pulmonary hypertension is 13.6% of OSA patients and 80% in overlap patients.[43] In another study the incidence was 36% vs. 9% in overlap and OSA respectively. The incidence of pulmonary hypertension in OHS patients is up to 50%.[44] Compare to OSA, overlap patients have higher plasma BNP level and new onset of atrial fibrillation.[45,46]

Compare to OSA, outcome studies on patients with OHS and overlap are very limited. Though there is a growing evidence of obesity paradox in metabolically healthy obese patients, morbidly obese patients with sleep disorder breathing are at risk of poor perioperative outcome. Patients with OSA has 2 times higher risk of pulmonary complications after non-cardiac surgery.[47] In bariatric surgical patients, the presence of OSA was found to be an independent risk factor for adverse postoperative events.[48] Flink et al. reported a 53% incidence of postoperative delirium in OSA patients vs. 20% in non-OSA patients.[49] A recent meta-analysis showed that the presence of OSA increased the odds of postoperative cardiac events including myocardial infarction, cardiac arrest and arrhythmias (OR 2.1), respiratory failure (OR 2.4), desaturation (OR 2.3), ICU transfers (OR 2.8), and reintubations (OR 2.1).[50] Compared with obese patients with eucapnia, OHS patients were more likely to develop heart failure (OR 9), angina pectoris (OR 9) and cor pulmonale (OR 9).[38] In patients with OHS with additional risk factors (previous history of venous thromboembolism, BMI ≥50 kg/m2, male sex, hypertension and age ≥45 years) undergoing bariatric surgery, mortality ranges between 2% and 8%.[51] A recent cohort study showed 90% of OHS patients were misdiagnosed and the 3-year mortality is worse than breast and colon cancer patients.[3] Another recent study on non-cardiac surgical patients showed that in comparsion with OSA patients, patients with hypercapnic OHS and overlap syndrome are more likely to experience postoperative respiratory failure (OR, 10.9), postoperative heart failure (OR, 5.4), prolonged intubation (OR, 3.1), postoperative ICU transfer (OR, 10.9), and longer hospital stay.[52] Metabolic syndrome is a risk factor for post-operative pulmonary complication, deep venous thrombosis, atrial fibrillation and congestive heart failure.[53,54] A recent outcome study on the bariatric surgical population showed that pulmonary complications and metabolic syndrome were significantly associated with increased postoperative mortality.[55]

TREATMENT

Initiating the treatment modalities in OHS patients is imperative to prevent the serious cardio respiratory and metabolic complications of OHS. The therapeutic goal is the normalization of the arterial carbon dioxide tension ($PaCO_2$) during wakefulness and sleep (i.e., $PaCO_2$ <45 mmHg). An multidisciplinary approach includes life style modification, positive airway pressure therapy and management of associated comorbid conditions. Life style modification includes dietary changes, exercise and behavioral modifications to obtain weight loss. Patients should be advised to avoid alcohol and sedative medications like benzodiazepines. Failure of weight loss with life style modifications necessitate bariatric surgery.

During this process initiating PAP therapy with CPAP or BPAP therapy based on the severity of associated OSA is the most important part to achieve the therapeutic goal. Pharmacological therapy with respiratory stimulants has potential side effects, it is considered for patients who continue to have serious hypoventilation despite positive airway pressure therapy. Long-term benefits of PAP include an improvement in pulmonary function and central respiratory drive to CO_2. Overall, bilevel PAP was not considerably superior to CPAP if CPAP titration was successful.[56] Average volume-assured pressure-support (AVAPS) ventilation is a new mode of PAP therapy which ensures the delivery of a preset tidal volume during bilevel PAP mode. Long-term PAP therapy also lowers the mortality rate in patients with OHS. A need for a backup rate should be strongly considered because central apneas occur commonly in patients with OHS undergoing PAP therapy. Supplemental oxygen is necessary for a group of patients with OHS who desaturate even with PAP therapy.[57] Both oxygen therapy without PAP therapy and higher concentration of oxygen can worsen the hypercapnia in OHS.[58]

Diagnosis of OSA and prescription of CPAP were associated with a reduction of postoperative cardiovascular complications.[59] The benefits of CPAP in surgical patients has been shown in a recent meta-analysis.[60] A diagnosis of OSA and use of CPAP therapy were related with a reduction

Table 2:
STOP-Bang Questionnaire

Yes	No	
○	○	**Snoring?** Do you **Snore Loudly** (loud enough to be heard through closed doors or your bed-partner elbows you for snoring at night)?
○	○	**Tired?** Do you often feel **Tired, Fatigued, or Sleepy** during the daytime (such as falling asleep during driving)?
○	○	**Observed?** Has anyone **Observed** you **Stop Breathing** or **Choking/Gasping** during your sleep?
○	○	**Pressure?** Do you have or are being treated for **High Blood Pressure**?
○	○	**Body Mass Index more than 35 kg/m²?**
○	○	**Age older than 50 year old?**
○	○	**Neck size large? (Measured around Adams apple)** For male, is your shirt collar 17 inches or larger? For female, is your shirt collar 16 inches or larger?
○	○	**Gender = Male?**

Scoring Criteria:

www.stopbang.ca
Property of University Health Network

For general population
Low risk of OSA: Yes to 0-2 questions
Intermediate risk of OSA: Yes to 3-4 questions
High risk of OSA: Yes to 5-8 questions
Yes to 2 of 4 STOP questions + individual's gender is male
Yes to 2 of 4 STOP questions + BMI > 35 kg/m²
Yes to 2 of 4 STOP questions + neck circumference male 17"
Female 16"

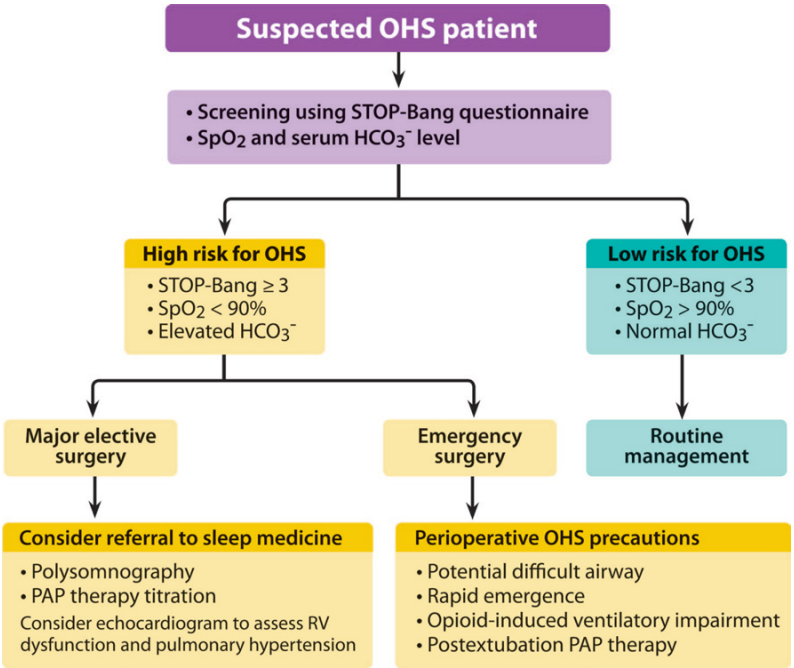

Figure: 2: Chau EH, et al. Anesthesiology 2012; 117:188-205

in postoperative complications especially cardiac arrest and shock.[61] Another recent study of 2000 OSA patients in 50 US hospitals found that OSA patients with CPAP treatment have less cardio-respiratory complications than OSA without CPAP therapy.[62] More time on CPAP reduces mortality in overlap patients.[63]

Preoperative Screening and Risk Assessment

Preoperative screening is the most important step in the management of any morbidly obese patient with OHS or overlap syndrome. Since most of these patients are not diagnosed or misdiagnosed, a screening tool with a high sensitivity is imperative. The definitive test to identify the daytime hypercapnia is blood gas analysis. Since it is invasive, other sensitive surrogate marker is an increase in serum bicarbonate level and a lower oxygen saturation. Increased serum HCO3- level caused by metabolic compensation with chronic respiratory acidosis is common in patients with OHS and other hypoventilation conditions. Obese patients with severe OSA and restrictive chest mechanics are more likely to have OHS.[64] Recent data shows an elevated serum bicarbonate without daytime hypercapnia can predict the early stage OHS among obese patients.[65] Also end-tidal CO_2 can be used as a substitute for ABG. Mokhlesi and colleagues suggested 3 clinical predictors of OHS: serum HCO3-, AHI, and lowest oxygen saturation during sleep.[66] In obese patients with OSA referred to the sleep clinic for suspicion of OSA, a serum HCO- threshold of 27 mEq/L demonstrated a 92% sensitivity in predicting hypercapnia on arterial blood gas.[66] To complement the highly sensitive serum HCO3-, a highly specific (95%) AHI threshold of 100 was identified. A 2-step screening process was proposed, with serum HCO3- as the initial test to exclude patients without OHS and then AHI as the second test to improve specificity (Fig 2). In addition, hypoxemia (SaO_2 <90%, corresponding to PaO_2 <60 mm Hg)[67] during wakefulness should lead clinicians to suspect OHS in patients with OSA.

Since polysomnography is a time consuming and expensive test, the STOP-Bang questionnaire (Table 2) may be used as a screening tool.[68] The STOP-Bang questionnaire has the highest methodological validity and reasonable accuracy in predicting a diagnosis of OSA[69,70] and a STOP-Bang score of 5–8 identified patients with a high probability of moderate-to-severe OSA.[71] The addition of serum HCO3- level ≥ 28 mmol/L to a STOP-Bang score ≥ 3 improves the specificity for preoperative obstructive sleep apnea recognition.[72] For obese or morbidly obese patients, a STOP-Bang score of 4 or greater can be used as a cut-off.[73] Oxygen Desaturation Index from a high resolution nocturnal oximeter is a sensitive and specific tool

Table 3: Perioperative Precautions and Risk Mitigation for OSA Patients

Anesthetic Concern	Principles of Management
Premedication	Avoid sedating premedication[56] Consider Alpha-2 adrenergic agonists (clonidine, dexmedetomidine)[57]
Potential difficult airway (difficult mask ventilation and tracheal intubation)[58,59]	Optimal positioning (Head Elevated Laryngoscopy Position) if patient obese Consider CPAP preoxygenation[62] Two-handed triple airway maneuvers Anticipate difficult airway. Personnel familiar with a specific difficult airway algorithm[61]
Gastroesophageal reflux disease[64]	Consider proton pump inhibitors, antacids, rapid sequence induction with cricoid pressure
Opioid-related respiratory depression[56]	Minimize opioid use Use of short-acting agents (remifentanil) Multimodal approach to analgesia (NSAIDs, acetaminophen, tramadol, ketamine, gabapentin, pregabalin, dexmedetomidine, clonidine, Dexamethasone, melatonin) Consider local and regional anesthesia where appropriate
Carry-over sedation effects from longer-acting intravenous and volatile anesthetic agents	Use of propofol / remifentanil for maintenance of anesthesia Use of insoluble potent anesthetic agents (desflurane) Use of regional blocks as a sole anesthetic technique
Excessive sedation in monitored anesthetic care	Use of intraoperative capnography for monitoring of ventilation[26]
Post-extubation airway obstruction	Verify full reversal of neuromuscular blockade[26] Extubate only when fully conscious and cooperative[26] Non-supine posture for extubation and recovery[26] Resume use of positive airway pressure device after surgery[26]

Adapted from Seet E, Chung F Can J Anesth 2010; 57: 849-64

to detect undiagnosed sleep disordered breathing in the surgical patients.[74] Patients with preoperative mean overnight SpO_2 <93%, or oxygen desaturation index >29 events/h were recently shown to be at higher risk for postoperative adverse events.[75]

The Obesity Surgery Mortality Risk Score was developed for patients undergoing gastric bypass, but it can be used for non-bariatric surgeries also. This includes 5 risk factors: hypertension, BMI of 50 kg/m^2 or greater, male sex, age 45 years or more, and known risk factors for pulmonary embolism (OHS, previous thromboembolism, preoperative vena cava filter, pulmonary hypertension).[76] This risk score stratifies mortality risk into low (0 or 1 comorbidity), intermediate (2 to 3 comorbidities) and high (4 to 5 comorbidities) with mortality of 0.2%, 1.2%, and 2.4% respectively.

Intraoperative Management

There is an increased recognition that obese patients present a different set of challenges and require specific peri-operative care due to the possibility of difficult intubation, difficult mask ventilation, increase sensitivity for opioids, associated comorbidity, intraoperative and post-operative cardio-respiratory complications. Recently, Society for Obesity and Bariatric Anaesthesia has published guideline on the perioperative management of obese patient.[77] During induction of general anesthesia, oxygen saturation falls more rapidly during apnea, which can be limited by a 25 degree head-up position during preoxygenation,[78] the combination of preoxygenation, nasopharyngeal oxygen insufflation,[79] and positive end-expiratory pressure (PEEP) of 10 cm H_2O.[80] The United Kingdom Fourth National Audit Project (NAP 4) reported a four-fold increase in the risk of serious airway complications in the morbidly obese patient.[81]. Positioning with the head, neck and shoulders elevated in the head elevated laryngoscopy position ("HELP") facilitates direct laryngoscopy. A neck circumference greater than 42 cm and BMI more than 50kg/m^2 is associated with an increased risk of difficult intubation.[82,83] There is conflicting evidence regarding the predictors of difficult intubation like neck circumference, severity of OSA, pretracheal soft tissue thickness and BMI.[84] Double-lumen supraglottic airways, such as the LMA ProSeal™ and the LMA Supreme™, provide higher leak pressures and may be safer in patients with obesity.[85] Videolaryngoscopic guided intubation has a high success rate in the morbidly obese patients with a difficult airway.[86] The use of awake video laryngoscopy-assisted tracheal intubation has also been described as an alternate to flexible bronchoscopic intubation.[87] According to the Difficult Airway Society published guidelines,[88] patients with obesity and OSA are stratified into a category of "at risk" of a major complication at extubation.

Morbidly obese patients need a protective ventilation with low tidal volumes (approximately 8 ml/kg) to avoid volutrauma and judicious use of oxygen to avoid absorption atelectasis.[89] Recruitment maneuvers (PEEP & Valsalva) can counteract these effects. Compared with the venturi mask, the Boussignac CPAP mask improves the postoperative PaO_2/FIO_2 ratio in morbidly obese patients.[90] A recent meta-analysis shows that recruitment maneuver added to PEEP compared with PEEP alone improves intraoperative oxygenation and compliance without adverse effects.[91] During bariatric surgery, pressure-controlled ventilation improves oxygenation compared with volume-control.[92] Perioperative auto-titrated continuous positive airway pressure treatment was shown to significantly reduce postoperative apnea hypopnea index and improved oxygen saturation in surgical patients with moderate and severe obstructive sleep apnea.[93] Since morbidly obese patients are prone to postoperative hypoxemia due to atelectasis, patients should be extubated wide-awake in the sitting position if possible.[94] Obese patient with OSA should have perioperative precautions and risk mitigation to achieve the best possible outcome (Table 3).

Regional anesthesia offers distinct advantages, which allows minimal airway manipulation, avoidance of anesthetic drugs with cardiopulmonary depression, reduced post-operative nausea and vomiting and reduced perioperative opioid requirements. However, the rate of block failure increased incrementally with a higher BMI.[95] Using ultrasound-guided regional anesthesia for peripheral nerve blocks in the obese population led to improved success rates.[96] Epidural analgesia should be considered in obese patients undergoing laparotomy to improve postoperative respiratory function.[97] Ultrasound guided neuraxial anesthesia is a viable option to increase the successes in obese patients.[98] A recent study on 40,316 patients with sleep apnea diagnosis who underwent hip and knee arthroplasty, the use of neuraxial anesthesia vs. general anesthesia was associated

with decreased odds for the need for mechanical ventilation, use of ICU, prolonged length of stay and cost.[99]

POST-OPERATIVE CARE

Morbidly obese patients with hypercapnia due to OHS or overlap syndrome have high possibility of post-operative respiratory failure. Though the evidences are limited in surgical population, in general these patients need to be admitted to intensive care or high dependency unit based on the risk assessment. Reassuming the PAP therapy in a diagnosed OHS or a suspected OHS in the immediate postoperative period is important to prevent respiratory failure. PAP was found to decrease respiratory failure after extubation in severely obese patients admitted to the intensive care unit (absolute risk reduction of 16%).[100]

In the postoperative period, these patients may decompensate acutely due to multiple factors, including sedation, sleep deprivation, and deconditioning.[101] Different presentations of acute cardiopulmonary failure in the postoperative periods are hypercapnic respiratory failure, acute congestive heart failure, acute cor pulmonale, and sudden death.[101] OHS patients are more prone for opioid induced ventilator insufficiency. An opioid-sparing analgesic regimen, including local anesthetic-infused nerve block catheters and nonopioid adjuncts (acetaminophen, nonsteroidal antiinflammatory drugs), should be considered in these patients. Recurrent respiratory events in the postanesthesia care unit, including apnea for 10 seconds or more, bradypnea of less than 8 breaths/min, pain-sedation mismatch, or desaturations to less than 90%, can be used to identify patients at high risk of postoperative respiratory complications.[102] Sedation level is a more reliable sign of opioids induced ventilatory depression than respiratory rate because multiple reports suggest that respiratory depression is not always accompanied by a decrease in respiratory rate.[103]

CONCLUSION

OHS and overlap syndrome are different conditions and both can cause hypercapnic respiratory failure and pulmonary hypertension. The interaction between these conditions is complex. Compare to OSA alone, OHS and overlap syndrome are rare but have higher perioperative morbidity. The evidence related to OHS and overlap in a morbidly obese patient is very limited. At the same time, the awareness about OHS and overlap syndrome are minimal among anesthesiologists. Since most of these patients are not diagnosed and the morbidity is higher than those with OSA, this poses a great challenge to the perioperative team. OSA patients with elevated bicarbonate and lower oxygen saturation need careful evaluation to rule out hypercapnic sleep disorder breathing conditions. A stringent care pathway is necessary to identify these high risk patients and further research is warranted in this area.

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Don't Make Things Worse with Your Ventilator Settings!

Peter Slinger, MD, FRCPC
Professor, Department of Anesthesia, University of Toronto

Historically, anesthesiologists have been taught to ventilate patients with relatively large tidal volumes in the perioperative period. Volumes as high 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] Recent studies have identified the use of large tidal volumes as a major risk factor for development of lung injury in mechanically ventilated patients without acute lung injury (ALI). Gajic reported that 25% of patients with normal lungs ventilated in an ICU setting for 2 days or longer developed ALI or Adult Respiratory Distress Syndrome (ARDS).[3] The main risk factors for ALI were use of large tidal volumes, restrictive lung disease, and blood product transfusion. A prospective study from the same group found that tidal volumes >700 mL and peak airway pressures >30 cmH_2O were independently associated with the development of ARDS.[4] An intraoperative study of patients undergoing esophageal surgery compared the use of tidal volumes of 9 mL/kg without PEEP during two- and one-lung ventilation vs. 9 mL/kg during two-lung ventilation and 5 mL/kg during one-lung ventilation with PEEP 5 cmH_2O throughout.[5] Significantly lower serum markers of inflammation (the cytokines interleukin 1ß [IL-1ß], IL-6, and IL–8) were found in the group receiving lower tidal volume plus PEEP. No major difference in postoperative outcome between the two groups was reported; however, the study was not powered to do this. The study did demonstrate better oxygenation in the lower tidal volume group during and immediately after one-lung ventilation, but not after 18 hours. In a study looking at conventional vs. protective ventilation in critically ill patients without lung injury, de Olivera and colleagues randomized patients to ventilation with either 10–12 mL/kg or 6–8 mL/kg predicted body weight.[6] In both groups, 5 cmH2O of PEEP was applied and the FiO_2 titrated to keep oxygen saturation above 90%. At 12 hours post-ventilation, inflammatory markers in broncho-alveolar lavage fluid (tumor necrosis factor-alpha [TNFα] and IL-8) were significantly higher in the larger tidal volume group. Choi and colleagues compared ventilation with 12 mL/kg without PEEP vs. 6 mL/kg with 10 cm PEEP and showed procoagulant changes in lavage fluid of the larger tidal volume group after 5 hours of mechanical ventilation.[7] A randomized controlled trial in 150 critically ill patients without ALI compared tidal volumes of 10 mL/kg vs. 6 mL/kg predicted body weight.[8] The conventional tidal volumes were associated with a sustained plasma increase in inflammatory cytokines.

Work suggesting that non-injurious, or so-called protective, ventilatory settings can induce lung injury in previously healthy lungs is also important. An animal study using a very elegant murine 'one-hit' VILI model showed that even least injurious lung settings induced biochemical and histological changes consistent with lung injury.[9] Work with rodents undergoing mechanical ventilation showed significant gene expression (including genes involved in immunity and inflammation) after only 90 minutes of protective ventilation.[10] Whether this has an impact on clinical outcome is unknown at this time.

ALI is the most common cause of postoperative respiratory failure and is associated with a markedly decreased postoperative survival rate.[11] A prospective case-control study by Fernandez-Perez and colleagues, looking at intraoperative ventilator settings and ALI after elective surgery in over 4,000 patients, showed a 3% incidence of ALI in high-risk elective procedures. Compared with controls, patients with ALI had significantly lower postoperative survival and increased length of hospital stay. Interestingly, in this study, intraoperative peak airway pressure, but not tidal volume, PEEP, or FiO_2, was associated with ALI. A retrospective cohort study looking specifically at intraoperative risk factors for ARDS in critically ill patients found that the odds of developing ARDS were 3 times greater for those receiving fluid resuscitation >20 mL/kg/h than if <10 mL/kg/h was given (odds ratio 3.1, 95% CI = 1.0–9.9, P = 0.05).[12] Tidal volume and the number of blood products were not associated with ARDS in this study. Of interest, the majority of patients were ventilated with a tidal volume, corrected for ideal body weight, of 8–10 mL/kg and an intraoperative PEEP of 0.

Ventilator-induced Lung Injury

The phenomenon of Ventilator-Induced Lung Injury (VILI) is well recognized and can be particularly significant in surgical procedures that require large transfusions or in cardiopulmonary bypass with associated lung ischemia-reperfusion injury. The deleterious effects of mechanical ventilation may be mediated by localized inflammation and the systemic release of inflammatory cytokines (biotrauma). Mechanical stretch from cyclical alveolar opening and closing sets up an inflammatory response in the alveolar and vascular endothelial cells. Hyperinflation causes nuclear translocation of nuclear factor kappa beta (NF-κB), a key regulator of the expression of multiple genes involved in the inflammatory response, and upregulation of other proinflammatory cytokines. Polymorphonuclear leukocyte recruitment and activation appear to be key components of the mechanical stretch-induced inflammatory response. The balance between apoptosis and necrosis is unfavorably altered by both ischemia-reperfusion and mechanical stretch.[13]

Biotrauma not only aggravates ongoing lung injury, it also has important systemic consequences owing to the spillover of these inflammatory mediators into the systemic

circulation, inducing remote organ dysfunction. A study looking at novel mechanisms of remote organ injury resulting from VILI showed that mechanical ventilation can lead to epithelial cell apoptosis in the kidney and small intestine with accompanying biochemical evidence of organ dysfunction.[14] In mice undergoing injurious mechanical ventilation, alveolar stretch was found to induce adhesion molecules not only in the lung, but also in the liver and kidney. In addition, cytokine and chemokine expression in pulmonary, hepatic, and renal tissue after mechanical ventilation was accompanied by enhanced recruitment of granulocytes to these organs.[15] These studies partially explain the remote organ dysfunction seen with ALI/ARDS and the role optimizing ventilatory strategies play in ameliorating it.

Intraoperative Ventilator-induced Lung Injury

Are the lung-protective strategies in ARDS[16] applicable to the intraoperative period, specifically in patients with healthy lungs? A paper examining this question highlights the lack of randomized controlled trials looking at best intraoperative tidal volume, PEEP, and use of intraoperative lung recruitment.[17] While outcome studies are lacking, based on what we know about the effects of mechanical ventilation, it seems reasonable to aim toward protective ventilatory strategies in perioperative practice. Three randomized controlled studies of patients undergoing major abdominal surgery have reached conflicting conclusions. A study by Treschan et al.[18] found no difference in respiratory complications with lower vs. higher tidal volumes. Two studies, one by Futier et al.[19] and another by Severgini et al.,[20] both found improved outcomes with lower tidal volumes. The important difference between these studies may be that in the first, both low and high tidal volume groups received PEEP, while in the latter two studies only the low tidal volume groups had PEEP. These findings await confirmation in larger studies.[21]

A study of one-lung ventilation for minimally invasive esophagectomy also found better pulmonary outcomes with lower tidal volumes and PEEP.[22] One-lung ventilation itself may be injurious to both the ventilated and the non-ventilated lung[23] and this injury depends on the duration of one-lung ventilation.[24] It may be best to avoid traditional one-lung ventilation whenever possible by applying continuous positive airway pressure to the non-ventilated lung.[25] This is a particularly attractive option during minimally invasive intrathoracic surgery that does not involve the lungs (i.e., cardiac, vascular, or esophageal surgery).

ALI after pneumonectomy is a well-known complication with a high mortality rate. Traditionally, the complication has often been blamed on the anesthesiologist's administering excess fluids during surgery. However, there is now evidence that this ALI is related more to the use of excessively large tidal volumes during one-lung ventilation than to fluids.[26] Although there has not been a convincing human prospective study on the use of small vs. large tidal volumes during one-lung ventilation, one large animal study clearly showed that the use of large vs. small (12 mL/kg vs. 6 mL/kg) tidal volumes, with the addition of PEEP 5 cmH_2O in the small volume group, resulted in a significant increase in lung water after pneumonectomy in the large tidal volume group.[27]

PERIOPERATIVE MANAGEMENT

Surgical Environmental Factors

Numerous factors in the surgical environment can contribute to lung injury, the most obvious being the surgical approach. Site of operation is an important predictor of pulmonary complications with upper abdominal and thoracic incisions (any surgery approaching the diaphragm) being the most important.[28] A decrease in respiratory complications has been documented if major cavity procedures can be done with minimally invasive vs. open techniques.[29,30] Atelectasis, a pathological state that can contribute to lung injury, occurs frequently following open surgical procedures and in up to 90% of patients undergoing general anesthesia.[31] Thus, anesthesiologists must be aware of techniques to avoid or treat it.[32] While open to debate, retrospective[33,34] and prospective[35] studies have shown that appropriate thoracic epidural analgesia reduces the incidence of respiratory complications (atelectasis, pneumonia, and respiratory failure) after major abdominal and thoracic surgery. The benefits of epidural analgesia appear to be directly proportional to the severity of the patients' underlying lung disease. Patients with COPD seem to derive the most benefit from epidural analgesia.[36] Although it has not been specifically studied in high-risk patients, reviews comparing paravertebral block vs. epidural analgesia in patients undergoing thoracic surgery showed equivalent analgesia efficacy but a better side effect profile and lower complication rate with paravertebral block.[37,38] In patients who develop early desaturation after major abdominal surgery, aggressive physiotherapy with continuous positive airway pressure in the postoperative period leads to lower rates of major respiratory complications.[39]

Role of Volatile Anesthetic Agents in Lung Protection

Volatile anesthetic agents have immune-modulatory effects. Much work has been done, especially in the cardiac setting, on the role of volatile agents in ischemia-reperfusion injury and in preconditioning and post-conditioning. Recent studies in models of ALI during one-lung ventilation and in cases of lung ischemia-reperfusion[40] suggest that volatile agents may act as pre- and post-conditioning agents, inducing lung protection by inhibiting the expression of pro-inflammatory mediators. Isoflurane pretreatment in an endotoxin-mediated animal model of lung injury exerted protective effects as evidenced by reduction in recruitment of polymorphonuclear leukocytes and microvascular protein leakage.[41] Post-conditioning with sevoflurane attenuated lung damage and preserved lung function in an in vivo rat ALI model.[42] In a prospective study, patients undergoing thoracic surgery with one-lung ventilation were randomized to either propofol or sevoflurane anesthesia.[43] Looking at inflammatory markers in the non-ventilated lung, the authors showed an attenuated inflammatory reaction with sevoflurane. Notably, the sevoflurane group had improved outcome and significantly lower adverse events overall. A study comparing one-lung ventilation with desflurane vs. propofol anesthesia examined the inflammatory response in the ventilated lung.[44] The inflammatory markers IL-8, IL-10, PMN elastase, and TNFα were significantly lower in the desflurane group. While much remains to be done, this exciting work does point toward a role for volatile agents in attenuating the pro-

inflammatory response in the lungs to a host of insults, whether this is before, during, or following the insult.

Fluids, Inflammation, and the Glycocalyx

It has long been a concern that excess amounts of intravenous fluids predispose patients to develop ALI. However, a conflicting concern for anesthesiologists is that fluid restriction in thoracic surgery may contribute to postoperative renal dysfunction, which previously was reported to be associated with a very high (19%) death rate.[45] A more recent retrospective study looking at all pulmonary resection patients found that acute kidney injury, as defined by Acute Kidney Injury Network criteria, occurred in 67 of 1,129 patients (6%) and was not associated with a statistically significant increase in mortality compared with patients who did not experience acute kidney injury (3% vs. 1%).[46]

Fluid requirements vary widely between patients and procedures, and ultimately represent the sum of preoperative deficits, maintenance requirements, and ongoing losses. Fluid management for major esophageal surgery is especially challenging.[47] If fluid intake has been limited by esophageal obstruction or dysphagia, patients undergoing esophageal procedures may be relatively hypovolemic after long preoperative fasts, which can complicate fluid management. Perioperative losses occur via a number of mechanisms including urinary, gastrointestinal, and evaporative losses, bleeding, and interstitial fluid shifting. This shift of fluid from the vascular compartment into the interstitial space accompanies surgical trauma and is likely to reflect vascular injury and loss of endothelial integrity. So-called "third space" losses describe fluid loss into non-interstitial extracellular spaces that are not in equilibrium with the vascular compartment, and thus are considered to be a "nonfunctional" extracellular fluid compartment. However, it is very possible that the "third space" does not exist, and was described as a result of measurement errors in early studies of the fluid compartments in the body.[48]

One of the factors complicating fluid management for esophageal resection is that thoracic epidural analgesia has been shown to improve outcome for these patients,[49] but its use tends to contribute to hypotension. Hypotension is well known to contribute to ischemia of the gut anastomosis,[50] and treatment with excessive fluids is likely to exacerbate the problem.[51] Many surgeons are concerned about the effects of vasopressors on anastomotic gut blood flow.[52] However, several animal studies suggest that treatment of intraoperative hypotension with norepinephrine does not cause any reduction of gut blood flow in the presence of normovolemia.[53,54]

An ideal fluid regimen for major procedures, including esophageal surgery, is individualized and optimizes cardiac output and oxygen delivery while avoiding excessive fluid administration. There is some evidence that fluid therapies designed to achieve individualized and specific flow-related hemodynamic endpoints such as stroke volume or cardiac index (collectively referred to as goal-directed fluid therapy) may provide a superior alternative to fixed regimens or those based on static measures of cardiac filling, such as central venous pressure, which do not predict fluid responsiveness or correlate with circulating blood volume after transthoracic esophagectomy.[55,56] However, fluid responsiveness remains an elusive goal for managing patients. As patients approach the upper inflection point of the Frank-Starling curve, small increases in cardiac output create large increases in lung water, and this effect is exacerbated in a situation of increased capillary permeability such as sepsis.[57] In addition to the potential importance of the amount and timing of fluid administration, there is some clinical evidence that the choice of fluid type may be important in affecting clinical outcomes[58] Intravascular colloid retention during treatment of hypovolemia may approach 90%, vs. 40% when administered during normovolemia.[48]

The relationship of hydrostatic and oncotic pressure to determine fluid flux across a semipermeable membrane, such as the lung capillary endothelium, was described in a classic equation developed in 1896 by Starling.[59] However, several subsequent clinical observations are not explained by the Starling formula, such as the intact organism's relative resistance to developing edema and the inability of therapy with hyperoncotic agents to draw fluid from the pulmonary interstitium into the vascular compartment.[60] This discrepancy is now attributed to the glycocalyx, a microcilial layer that lines the endothelium and acts as a molecular sieve.[61] This layer tends to increase the oncotic pressure on the inner surface of the endothelium and decrease leukocyte and platelet adhesion to the endothelium. The glycocalyx deteriorates during ischemia-reperfusion injury and in the presence of a wide variety of inflammatory mediators such as cytokines, which probably contributes to the increased vascular permeability seen in these situations. Also, the glycocalyx deteriorates in the presence of atrial natriuretic peptide, which may explain the increase in plasma protein filtration that has been seen with colloid boluses. Protecting the glycocalyx may be among the anesthesiologist's most important duties in the perioperative period. Volatile anesthetics may have a protective effect on the glycocalyx.[62,63]

SUMMARY

Anesthesiologists manage a heterogeneous group of patients in the perioperative period, from those with healthy lungs or "at risk" lungs to patients with established ALI/ARDS. More patients are at risk for ALI during and after surgery than previously thought. Appropriate perioperative management may prevent or ameliorate this lung injury. Are the proven lung-protective strategies in ARDS applicable to the perioperative environment, specifically in patients with healthy lungs? Although evidence from randomized controlled trials is lacking, applying protective ventilatory strategies in the intraoperative period seems reasonable based on our current understanding of mechanical ventilation and lung injury. Apart from ventilation strategies, the anesthesiologist also needs to be concerned about fluid management and prevention of systemic inflammation as vital aspects of lung protection.

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Update on Thoracic Epidurals: Risk vs. Benefits?

Hendrik Freise, MD
Hugo K. Van Aken, MD
Department of Anesthesiology and Intensive Care Medicine, University Hospital Muenster, Muenster, Denmark

Summary Statement: Thoracic epidural anaesthesia reduces perioperative mortality and morbidity. To increase safety of the procedure the risk of epidural bleeding and infections must be strictly controlled and effective algorithms of treating side effects and complications are necessary.

SUMMARY

Beyond excellent pain therapy thoracic epidural anaesthesia (TEA) influences perioperative function of vital organ systems. A recent meta-analyses suggest that TEA decreases cardiac morbidity and mortality after cardiac and major non-cardiac surgery. TEA seems to improve intestinal perfusion in major surgery when systemic hemodynamic effects of TEA are adequately controlled. TEA augments recovery of intestinal transport function after major laparoscopic surgery, whereas effectiveness is questioned in a setting with minor surgery and a fast track surgery regimen. Independent of superior pain control the impact of TEA on the perioperative pathophysiologic changes seems to be procedure specific. Retrospective studies and meta-analyses suggest reduced mortality in patients treated by TEA. Control of hypotension is necessary.

Epidural bleeding can be reduced by strict adherence to safe time intervals to the application of concomitant anticoagulants. Aspirin-prophylaxis alone must not be ceased solely to perform TEA. Infectious complications are rare and associated with better prognosis. Close neurologic monitoring is mandatory in every patient treated with TEA. Risk/benefit-balance of TEA is favourable and should foster clinical use.

Keywords: cardiovascular risk, epidural anaesthesia, infection, intestinal, bleeding

INTRODUCTION

Thoracic epidural anaesthesia has a widespread use in the perioperative care after thoracic and major abdominal surgery providing high quality analgesia[1,2]. Due to excellent analgesia and numerous effects on neurohumoral and autonomic nervous system response to surgical stress it might influence postoperative cardiovascular, intestinal and immune function, ultimately resulting in improved outcome[3-6]. However, as an invasive technique TEA inevitably carries the risk of specific complications even when contraindications are properly considered. There is an ongoing debate whether these risks of TEA and its consumption of procedural resources in the perioperative period are worth the benefits with respect to outcome and organ protection.

This review will highlight the perioperative risks related to TEA as well as the benefits of TEA with respect to the cardiovascular system, the intestinal tract and the host immune response to the perioperative spread of malignant cells.

Increased Sympathetic Activity and the Stress Response

Stress usually inflicts distinct changes in the host's hormonal and immune response as well as the coagulation system[7,8]. Stress is caused by a multitude of situations of physical danger or factual injury to the organism but also can be induced solely by emotional tension or fear of adverse events[9-11]. The stress response, which has been highly conserved throughout evolution, can turn against the host in the case of coexisting cardiovascular disease. In these patients, even watching a soccer game lastingly increases the risk of acute coronary syndromes and significant arrhythmia[12].

There are different synergistic mechanisms involved in cardiac complications during stress. Increased catecholamine levels increase afterload of the left ventricle. Tachycardia further increases workload of the heart while decreasing the time for coronary perfusion[13]. While healthy coronary arteries relax to compensate for the higher need of oxygen, altered and stenotic coronary arteries are not able to relax or even constrict on sympathetic stimulation[14,15]. Raised Corticotropin-Releasing-Hormone-levels reduce cardiac NO-release and increase the endothelin production. This aggravates coronary endothelial dysfunction[16]. Stress can induce a pro-coagulatory state in the absence of any trauma[17]. This effect is prolonged with increasing age[18]. Finally, the early phase of stressful events is characterized by a proinflammatory response that may lead to plaque instability via the activation of matrix-metalloproteinases[19]. This fatal triad triggers acute coronary syndromes and myocardial infarction during and after stressful events.

In the perioperative period, surgery and related interventions induce stress responses. Endotracheal intubation alone has been shown to be related to a marked increase of norepinephrine and prolactin[20,21]. Both after minimal invasive and major open surgery increased serum levels of stress hormones were recorded[22,24]. A pro-coagulant state has been repeatedly shown after major abdominal and orthopaedic surgery and persists weeks after surgery[23,25,26]. As a consequence of this constellation, cardiovascular mortality accounts for 63% of perioperative mortality in a high risk patient population and is still responsible for 30% of perioperative mortality in low risk patients[27].

TEA and Sympathetic Block

TEA has been intensively investigated with respect to its effect on perioperative pathophysiology and outcome. In the scientific discussion, segmental temporary sympathetic block is assumed to be related to the beneficial effects[6,28]. However, both clinical and experimental data on sympathetic activity

during TEA are scarce and needs careful interpretation. Methodological limits of sympathetic activity measurement as well as the level of epidural catheter insertion, volume and concentration of local anesthetics needs to be considered[29,30].

Microneurography is the only technique that allows direct quantitative insight into abdominal sympathetic activity and allows the discrimination between muscle and skin sympathetic activity. It is, however, highly limited in spatial resolution and restricted to animal experimental studies[31-33]. Many data were derived from indirect techniques such as skin conductance response and heart rate variability, relying on measurements of altered effector organ function during sympathetic block[31,34,35]. Most measurement, however, are based on assessment of skin perfusion. These parameters are, however, prone to affection by microvascular anatomy, emotional and thermoregulatory state or the presence of general anaesthesia[31,36,37].

Depending on the level of insertion, the segmental sympathetic block includes cardiac sympathetic efferent fibres in high TEA and splanchnic sympathetic nerves in the case of midthoracic TEA. The sympathetic block is supposed to be restricted to a segmental block with compensatory increased sympathetic activity in the segments below the intended block. This concept is based on two microneurographic studies in cats and rabbits conclusively demonstrating abdominal sympathetic block when mid-thoracic sympathetic roots were covered by TEA[33,38]. A thoracic sympathetic block was preoperatively demonstrated by thermography in TEA induced by low concentration and high volume of local anesthetic[39]. During midthoracic TEA, the decrease of skin temperature in Th4 – Th12 was significantly less pronounced compared to sham group, demonstrating reduced sympathetic vasoconstrictive activity. In a recent study, a cardiac sympathetic block was demonstrated for 6 days during patient controlled epidural anesthesia after esophagectomy[40]. Similarly, in a rat model of continuous TEA an early and sustained increase in skin temperature in the dermatomes Th1, Th6 and Th12 was recorded[29]. In another rat model, 30µl Lidocaine 2% injected epidurally at the level of Th6 induced increase in thoracic and abdominal skin temperature as qualitatively demonstrated by thermography[36]. In contrast to this, a clinical study failed to show thoracic sympathetic block within the sensory block in TEA using 4.2 ml Bupivacaine 0.75% injected at Th6-Th9[41].

However, it is still unclear whether a limited segmental thoracic sensoric block is accompanied by a limited sympathetic block. In experimental TEA in cats, high TEA with 0.1ml/kg Lidocaine 1% induced cardiac sympathetic block (Th1 – Th4) and reflectory increased renal sympathetic nerve activity (Th8) as recorded by microneurography. Vice versa, in the same study lumbar epidural anaesthesia (LEA) induced renal sympathetic block and increased cardiac sympathetic block via baroreceptor-reflexes. There are no data concerning sensoric block in this model[33]. Clinical data on a restricted segmental block of sympathetic activity in TEA is inconclusive until today. In human, limited upper thoracic sensoric block reaching Th6 occurred during high TEA induced by 4.2 ml Bupivacaine 0.75%. In these patients, however, skin temperature in the feet also increased, suggesting unrestricted sympathetic block including splanchnic and leg sympathetic nerves[41] In contrast to this, 4 ml Bupivacaine 0.5% injected at Th4 induced sensory block down to Th8 but did not affect sympathetic activity in the lower legs[31]. Consequently, the concentration of local anesthetic might not only determine the intensity but also extent of the sympathetic block[41,42]. A higher volume of Bupivacaine 0,25% injected at a midthoracic level induced a sympathetic block including the complete sympathetic innervation of the leg[39].

Anti-Ischemic Effects of TEA in Cardiac and Non-Cardiac Surgery

TEA has been repeatedly shown to decrease adverse perioperative cardiac events[4,43,44]. A superior pain relief with concomitant reduction of the postoperative stress response and systemic sympathetic activity is most likely to contribute to this effect[1,45,46]. Furthermore, regional sympathetic block including cardiac sympathetic nerves reduces not only ischemic pain but preserves coronary perfusion during cold pressor testing. This effect was most pronounced in stenotic vessels[47,48]. These data support findings of perioperative anti-ischemic effects of TEA both in cardiac and in non-cardiac surgery. TEA reduced diastolic dysfunction in patients with CAD undergoing operative revascularization[49]. Diastolic dysfunction has been reported to be an early sign of cardiac ischemia. While in this study no effect on systolic function was recorded, an earlier study revealed improved systolic function and wall motion in coronary artery disease. Troponin release and long term survival after CABG underline the cardioprotective potential of TEA in that study[50]. In experimental myocardial ischemia TEA reduced infarct size[13]. Due to the low incidence of complications and limited study sizes, one meta-analyses failed to prove decreased myocardial infarction after TEA in cardiac surgery[51,52]. However, a recent meta-analysis showed a decreased rate of combined end-points myocardial infarction and mortality after cardiac surgery in the presence of neuraxial blockade[51]. Furthermore, in non-cardiac high risk surgical patients continuous TEA prevented myocardial infarction[43].

Intestinal perfusion – A matter of Hemodynamic Control

Safeguarding intestinal perfusion is a critical issue in the maintenance of intestinal function and integrity of mucosal barrier. TEA reversed impaired intraoperative intestinal oxygenation during major surgery and protected intestinal barrier function in experimental hypoxemia[53,54]. In acute experimental pancreatitis and in sepsis TEA improved mucosal capillary perfusion[55,56]. In healthy rats a shift from intermittent to continuous capillary perfusion in the face of mild hypotension was recorded during TEA[57]. Similarly, in patients undergoing esophagectomy continuous epidural infusion of Bupivacaine without a bolus dose increased anastomotic mucosal blood flow compared to the control grou[58]. In these studies, TEA was associated with no or only moderate hypotension. After esophagectomy the postoperative increase in cardiac output during the weaning procedure was blunted by TEA, thereby suggesting effective sympathetic block with maintained hemodynamic control[58]. Most recently a small study reported selective improvement of gastroesophageal anastomotic perfusion in case of effectively maintained blood pressure[59].

However, a number of clinical and experimental studies revealed adverse effects of TEA on parameters of intestinal perfusion[60-63]. Only recently in 10 patients undergoing esophagectomy TEA has been demonstrated to reduce laser Doppler flow in the distal gastric tube mucosa[64]. All these studies reported substantial deterioration in systemic hemodynamic parameters. Mean arterial pressure was reduced by 20 – 50 % after induction or during maintenance of TEA[60,61,63,64]. Cardiac output remained stable in only one of these studies[63], but was decreased up to 35% in two other[60,64]. Furthermore, as far as data are provided, the animal experimental studies revealing adverse perfusion effects of TEA are related to an extended or total sympathetic block[60,61]. The clinical study described a sensoric block reaching Th4[62]. Since sympathetic block has been found to exceed sensoric block in epidural anaesthesia and sympathetic preganglionary neurons origin not higher than Th1, the sensoric level of Th4 suggest an almost complete craniocaudal sympathetic block in these patients[39].

In conclusion, TEA seems to exert beneficial effects on intestinal perfusion as long as its hemodynamic consequences are adequately controlled.

Intestinal Motility

Postoperatively, paralytic ileus and abdominal sepsis are life-threatening to the patient and have tremendous economic impact[65]. Pain, increased sympathetic tone, the use of systemic opioid analgesia and intestinal neuroinflammatory processes contribute to intestinal hypomotility[66]. The available data on postoperative intestinal function during TEA is a mosaic of small studies including both thoracic and LEA, different epidural drug regimens with or without epidural opioids and covering a wide range of surgical procedures. These studies has been analysed in a set of meta-analyses in the last decade[67-70]. In 2007 a systematic update did not retrieve any major study (group size >100) addressing intestinal function as primary or secondary outcome[71]. These meta-analyses showed accelerated recovery of intestinal function in all cumulated studies and subsets of studies in major vascular and colorectal surgery[67,68,70]. TEA resulted in a faster resolution of postoperative ileus after major non-intestinal surgery als[72]. In contrast to this, after not further specified intraabdominal surgery no improvement of intestinal function was found. The epidural infusion of local anaesthetics alone or in combination with epidural opioids were shown to be equally effective in accelerating intestinal recovery and superior both to systemic and to epidural opioids alone[67,73,74]. The faster resolution of postoperative ileus after major open surgery has been attributed to superior pain therapy, reduced opioid consumption and sympathetic block[67,71].

In the last decade systemic lidocaine emerged as a new comparator to epidural anaesthesia. In a direct comparison to lidocain-PCIA, epidural application of lidocaine was shown to be more effective concerning pain control and resolution of hypomotility after colonic surgery[75]. However the existing evidence is not sufficient to assess the value of lidocaine in the perioperative settting[76].

Anastomotic Perfusion and Patency

The impact of TEA on anastomotic perfusion and healing of anastomosis is still unclear.

In colorectal surgery TEA has been found to decrease anastomotic blood flow and improved gastric and transverse colonic blood flow[62]. After esophagectomy, reduction in the already compromised mucosal circulation of the oral end of the gastric tube was more pronounced compared to the aboral end[64]. In both studies, however, significant systemic hemodynamic alterations were present. In contrast to this, 1h (sedated patients) and 18h (awake and extubated patients) anastomotic mucosal blood flow was increased in TEA after esophageal resection[58].

Data on anastomotic patency is also equivocal until today. In 2001 a meta-analysis cumulated the evidence of 12 clinical trials comparing epidural and systemic analgesia with respect to anastomotic breakdown[77]. Only two of these studies included more than 30 Patients in each group. The epidural drugs differed between the studies and both lumbar and thoracic epidurals were tested in different surgical procedures. Additional four small studies compared different epidural drug regimens. As a result of this heterogeneity, neither impaired nor improved healing of anastomosis during epidural anesthesia was proven. In two larger retrospective case-control-studies including 259 mixed GI-anastomoses and 400 rectal cancer resections no influence of epidural anesthesia was proven[78,79]. In the most recent metaanalysis of perioperative outcome of epidural anesthesia anastomotic leakage was not found to be influenced.[4]

After almost a decade with no randomized controlled trial addressing the question of anastomotic patency, only recently TEA was shown to reduce the rate of anastomotic insufficiency after emergent laparotomy[80]. Furthermore a retrospective analysis of esophageal anastomosis, demonstrated a 70% risk-reduction for anastomotic leak in the TEA group[81]. This protective effect might be of tremendous importance in the light of the five-fold increase in mortality in patients with anastomotic leak. Nevertheless, still conclusive randomized controlled trials are needed. Due to the low incidence a large patient population will be needed.

TEA in the era of ERAS

Multimodal approaches to improve the outcome after surgery are increasingly implemented and recommended in numerous procedures[8,82]. The use of TEA in the setting of fast-track-regimen and minimal invasive approaches for major procedures has been questioned[71,83,84]. However, already now it is well documented, that TEA improves quality of postoperative pain control – which is the primary goal of any analgetic intervention – and improves bowel motility even in the setting of low level of surgical aggression[83,85].

Further studies of are needed to define the role of TEA in comparison to peripheral techniques such as transversus abdominis plane block or wound catheters[70].

TEA and Outcome

TEA provides superior pain therapy in a wide range of thoracic and abdominal surgery[1]. However, irrespective of better pain control improvement of the clinical postoperative course by TEA seems to be procedure specific. While effectivity of TEA in open colonic resection is well documented little benefit is reported after hysterectomy. However, in both

procedures a significantly improved pain control in TEA was reported, lasting up to two weeks after surgery[83,86,87]. Superior pain therapy and ameliorated metabolic response are related to improved quality of life after colonic resection[88,89]. A meta-analysis of pulmonary effects of TEA revealed a reduced rate of pneumonia after TEA, most probably due to earlier mobilisation, reduced opioid-consumption and improved coughing[3]. Two recent clinical studies revealed conflicting result with respect to pulmonary complications after esophagectomy and pneumonectomy[90,91]. In a most recent meta-analysis both atelectasis formation and incidence of pneumonia was decreased when epidural anesthesia was applied[4].

Rodgers and coworker demonstrated a 30% relative risk reduction of fatal outcome after surgery in unselected patients with neuraxial anaesthesia. The evaluation included LEA and spinal anaesthesia[44]. These findings were corroborated by Wu, who retrospectively demonstrated reduced mortality in the TEA-group after colectomy and lung resections[92,93]. In cardiac surgery an actual meta-analysis shows reduction of the combined outcomes myocardial ischemia and mortality, reduced renal failure and reduced need for ventilation in TEA for cardiac surgery[51]. While a recent study demonstrated reduced early morbidity after Off-pump cardiac surgery, a larger study including >600 patients with or without epidural anesthesia during cardiopulmonary bypass did not demonstrated differences in long term outcome[94,95].

In a detailed metaanalysis Pöpping and coworkers demonstrated a decrease of mortality in non-cardiac surgical patient treated with TEA for at least 24 h perioperatively. The number needed to treat was calculated to 1:90 epidurals to save one life[4].

Two retrospective analyses of the POISE 1 (Perioperative beta receptor blockade) and the POISE 2 (perioperative ASA and clonidine) databases revealed equivocal results.[96,97] In the POISE 1 population patient receiving TEA plus general anesthesia were found to be at higher risk of adverse outcome. This finding was based on the analysis of propensity matched pairs of patients. In the POISE 2 patient population a similar analysis this effect was not found anymore. In the POISE 1 population hypotension (incidence 14 – 28%) was accused to account for increased mortality. In the POISE 2 population incidence of clinically significant hypoptension was found in up to two third of all patients[96]. This increase in reported hypotension is most probably explained by the changes in definition of hypotension[98,99]. In POISE2 vasopressor use was included in the definition of relevant hypotension This might suggest, that the increased awareness and adequate treatment of hypotension improve safety of TEA. These equivocal results prompt the authors of the two analyses to underline the potential problem of retrospective data analysis and the need for prospective randomized data

Outcome Effects of TEA and LEA – Different Procedures, Different Effects

In contrast to TEA, LEA evokes different reactions of the autonomous nervous system. In a clinical study EDA induced by injection of 14 ml 2% mepivacaine at the level of L4/5 induce an increase in upper body sympathetic tone as recorded by blood pressure and heart rate variation[100]. This effect was not present in higher EDA at the level of L1/2. Similarly vascular tone in the upper extremety increases in LEA[101]. These clinical findings are supported by experimental studies in rabbits[38].

The lack of intestinal and cardiac sympathetic block corresponds to the lack of outcome improvement in LEA.[4]

TEA and Tumor Spread

Tumor resection is a most important therapeutic strategy in the cure or control of malignant diseases. However, the procedure carries oncologic risk for the patients. Surgical manipulation promote systemic spread of tumor cells, which predicts a poor outcome[102,103] The influence of surgical stress on the immune function impairs the host´s ability to eliminate the circulating tumor cells. This includes suppression of Natural Killer cell function, increased Th2-T-cell-activity and reduced innate immune reactivity[104]. These studies attracted attention to regional anaesthesia as a potential tool to influence long-term outcome by perioperative measures[105].

In the beginning four retrospective studies demonstrated reduced tumor recurrence rate and improved survival after regional anaesthesia in important tumor entities[106-109]. Additional retrospective data from colonic surgery suggest that age might influence the effects of TEA on cancer recurrence[110]. Morphine has been repeatedly shown to reduce Natural Killer cell activity and to promote growth in experimental colonic cancer metastasis and experimental breast cancer[111-114]. Hypothermia and adrenergic response also promote experimental tumor growth[115]. Tumor growth can be prevented by effective sympathetic block and analgesia in mice[116]. The observed protective effects of regional anaesthesia might be therefore based both on an opioid-sparing effect and on reduced neurohumoral stress response[117].

In the meantime numerous retrospective analyses were published in this field. However, we still lack large randomized clinical trials. Since numerous trials are recruiting we await a lot more data in the near futur[118].

Risks of TEA

The benefits of TEA can be demonstrated in large Patient populations only. An uneventful perioperative course can never be attributed solely to the use of TEA. The complications, hovewer, are highly specifically attributable to TEA. Complications might leave the patients severely impaired by spinal cord injury and result in forensic problems for the responsible anaesthesiologist. Consequently, patient safety issues are a dominant aspect in the clinical use and in patient perception of TEA. This characteristic constellation is different from other measures of perioperative care. The perioperative beta-blocker therapy as tested in the POISE-trial, for example, left 1 of 98 treated patients dead or with persistent neurologic deficit[99]. This risk exceeds that of TEA by magnitude, but its manifestations are far more unspecific and usually not clearly related to the therapeutic intervention. This constellation leads to precautions to use TEA in critical patients, although they might profit most[119].

There are three major risk categories to be considered: a) epidural bleeding, b) the unnecessary withdrawal of low dose aspirin in cardiovascular or cerebrovascular risk patients and c) epidural infection.

Epidural Bleeding in TEA and LEA – Different Procedure Different Risk

Until today, the risk of bleeding complications both after epidural anesthesia in general and specifically after TEA is not known. However, there is increasing evidence, that the overall number of epidural haematoma after epidural block might be misleading in clinical decision making. The overall incidence of epidural bleeding in the 1990-ies was 1:18,000 in the retrospective analysis of approximately 250,000 epidural blocks in Sweden[120]. This number, however, includes the obstetric epidural blocks. The latter patient population carries an extremely low risk of epidural bleeding after epidural puncture both in the retrospective analysis and the most recent prospective National Audit Project 3 in the UK[121,122]. The risk of epidural bleeding in the perioperative patient population in the retrospective study was consequently much higher, reaching a risk of 1:10,200 for surgical patients. Again, this number from Sweden strikingly well matches the prospective NAP3-data. In that study, the estimated risk of epidural haematoma ranged between 1:5,747 (pessimistic estimation) and 1:12,195 (optimistic estimation) in the perioperative population[123]. In recent single center database analyses the incidence of epidural bleeding and injury ranged between 1:2,700 and 1:4,761[1,120,124].

All these numbers, however include both LEA and TEA. In the swedish study 8 TEAs caused epidural haematoma as compared with 17 bleedings after lumbar epidural punctures[120]. However, it is not clear how often the respective procedures were performed. Thus, estimation of the risk of TEA is not possible. In NAP3 even 5 out of 8 bleeding complications occurred after TEA, but again the underlying numbers of TEA and LEA are not available. Assuming a less frequent use of TEA, the authors estimate a far higher risk of bleeding complications in TEA compared to LEA. This notion is supported by the retrospective analysis of 8100 patients. In this population 3 epidural haematoma occurred after TEA while no bleeding occurred after LEA. The numbers of the respective procedures, however, are not provided[124]. In contrast to this, no epidural bleeding was reported in 10,000 TEA, while all 3 reported bleedings occurred in LEA resulting in a risk of 1:832[1]. Furthermore, patient age and sex seems to be a major influencing factor of vertebral column haematoma after TEA.[1,120] In contrast to these studies, in a case series of 3736 orthopaedic patients, predominantly elder women, no bleeding complication were reported[125]. The higher risk of elder persons might be related to different causative factors such as reduced epidural space or degeneration of the spine, resulting in more frequent traumatic puncture. However, most important might be the high rate of concomitant use of anticoagulant or antiplatelet drugs in combination with (unrecognized) impairment of renal function. Consequently the available data allow a reasonable estimation of the overall bleeding risk of epidural anaesthesia but do not allow valid conclusions on the incidence of bleeding complications in TEA.

In two recent single center case series the risk of dural puncture[126] and the risk of temporary neurologic deficits was increased at the lumbar level[127]. In the former case series the only epidural hematoma in 5300 patients occurred after lumbar epidural puncture.

Pre-existing coagulation disorders and the use of anticoagulant or antiplatelet drugs are the most prominent risk factors of perioperative epidural haematoma. Furthermore, aged patients are at increased risk of epidural complications, most probably due both to age related alterations of spinal anatomy and to impaired renal function with unexpectedly prolonged drug effects. For example, even a mild impairment of renal function increase the time of effective anticoagulation by low molecular weight heparin (LMWH) from 6.6 to 9.9 hours. In case of severe chronic kidney disease LMWH effect lasts more than 15 hours[128]. In these patients a 50% dose reduction of LMWH is required. Renal function can be assessed by the MDRD formula. However, most elective surgical cases are hospitalized not longer than one day prior to surgery. Consequently, prophylactic anticoagulation is most often not necessary before insertion of epidural catheters. This ensures maximal safety of TEA even in elderly patients with decreased renal function.

When TEA is planned in patients using other antiplatelet or anticoagulant drugs, specific time intervals should be kept between the last medication and both catheter placement and catheter removal as reviewed earlier in detail[129,130]. Since catheter removal is a critical phase with increased incidence of epidural bleeding, neurologic surveillance must be assured until 24 h after catheter removal. This notion is emphasized by recent data from the UK reporting delayed diagnosis in 4 of 5 cases of epidural haematoma with persistent harm. Only one patient was treated in time and reached full recovery[123].

Withdrawal of Aspirin in the Post POISE 2 Era

In the western countries approximately 1.8 million coronary stents are implanted each year[131] and 500.000 strokes occur annually in the European union[132]. The high incidence of cardiovascular and cerebrovascular diseases in surgical patients results in an increased use of antiplatelet and anticoagulant drugs for secondary prophylaxis in patients scheduled for TEA.

The withdrawal of antiplatelet drugs leads to rebound effects with increased rate of thromboembolic events[133-135]. This rebound effect is aggravated by the prothrombotic and proinflammatory state induced by surgery[136]. In case of antiplatelet drug discontinuation within 3 weeks after stenting, mortality is to 30 - 86%[131]. Late stent thrombosis after antiplatelet drug discontinuation can occur more than one year after stenting[137,138]. Consequently it has become consensus to continue antiplatelet medication prescribed for primary and secondary cardio- and cerebrovascular prophylaxis in most surgical cases. Only in emergency intracranial, spinal and intraocular surgery, in which bleeding is potentially catastrophic, cessation and bridging with tirofiban and Heparin is recommended[131,139].

In the POISE 2 trial the aspirin continuation stratum was formed and randomized to aspirin and placebo in the perioperative period.[98]. The trial did not show an increased risk of nonfatal myocardial infarction or death while risk of surgical site bleeding was increased. However, only a minority of the POISE study population took ASA as primary or secondary prevention. Thus the risk of ASA cessation in this high risk population still can´t be definitively assessed[139]. Therefore, the use of perioperative TEA should not lead to

cessation of low dose acetylsalicylic acid prescribed for primary and secondary prophylaxis. There is most probably no increase in the rate of spinal epidural haematoma during low dose ASA intake[129]. However, the combination of ASA with other prophylactic anticoagulant or antiplatelet drugs must be excluded in case TEA is planned. Standard operating procedures assuring the beginning of thromboembolic prophylaxis after surgery are suitable to increase the safety of TEA in patients on ASA-prophylaxis.

While ASA is regarded as safe antiplatelet therapy, thienopyridine derivates such as clopidogrel are not recommended 5-7 days before TEA. This warning is based on the increased incidence of surgical bleeding under thienopyridines and the report of two cases of epidural haematoma after neuraxial block during clopidogrel medication[129,140]. Recently, however, a case series of 309 vascular surgery patients treated with LEA[141]. 217 of them were on dual platelet aggregation inhibition with additional ASA. None of these patients showed a sign of epidural or spinal bleeding. There are two cases of epidural catheter removal after commence of a dual antiplatelet therapy due to postoperative myocardial infarction[142,143]. An uneventfuls course after spinal anesthesia during dual antiplatelet therapy has been described earlier[144]. In contrast to this an increasing numbers of case report of spontaneous spinal hematoma during dual antiplatelet therapy without any anesthetic manipulation raises serious concerns[145-147]. Additionally, spontaneous spinal haematoma were described both in clopidogrel and in ASA alone[148,149] Consequently, the case series must not lead to mistake them as an evidence of safety.

Infectious Complications

TEA is an invasive analgesic technique and as such inevitably associated with the risk of local infectious complications. Iatrogenic pathogen inoculation and haematogenous infection of the insertion site or the epidural catheter are the potential causes of infection within the vertebral canal[150]. Estimates of incidence vary widely[150]. Recent data from Germany report an incidence of 1 abscess in 10,000 patients with TEA[1]. In the UK an incidence of 1:24,000 epidural abscesses was found after perioperative neuraxial blockade with 10 of 13 cases in the study period related to epidural anaesthesia[123]. In pediatric postoperative pain therapy epidural infections and abscesses are also rare[151]. Epidural abscess with spinal cord and radicular compression is the predominant complication after TEA and usually caused by staphylococcus aureus. Meningitis has also been reported with a lower incidence. It is usually caused by streptococcus species[150,152]. Infectious complications may occur as early as day 2 but usually present beginning from day 4 or later. They are often, but not always, accompanied by signs of infection of the insertion site and most often present with incomplete or unspecific symptoms. This frequently results in delayed diagnosis and underlines the necessity of close clinical observation and high level of suspicion[123] . The prognosis of infectious complications is better than that of epidural bleeding. All patients with meningitis reached full recovery and approximately 50 % of patients with epidural abscesses recover without permanent disability.[123]

CONCLUSIONS

TEA provides optimal pain therapy in a wide range of surgical procedures and reduces perioperative morbidity and mortality after major abdominal and thoracic surgery. Furthermore TEA might influence tumor progression after oncologic surgery. However, due to the low overall incidence of postoperative complications in many surgical procedures procedure-specific evidence-based recommendations concerning TEA are still hard to make. Rigid adherence to standard operating procedures and a continuously high level of suspicion can largely improve the safety of TEA in the face of antiplatelet and anticoagulant drugs.

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Patient Selection for Ambulatory Surgery: Can Any Patient Be an Outpatient?

Girish P. Joshi, MBBS, MD, FFARCS
Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, Texas

CASE

A 65-year-old male with a BMI of 43.5 kg/m2, history of heavy snoring and daytime somnolence, diabetes mellitus, and hypertension is scheduled for a hernia repair at a free-standing ambulatory surgery center (ASC). His medications include metformin and an ACE inhibitor. His vital signs and fasting blood sugar and HBA1c levels are within normal limits. Is this patient suitable to undergo a laparoscopic cholecystectomy in a free standing ASC?

A 57-year-old female with a BMI of 39.9 kg/m2 is scheduled for ureteroscopy, ureteral stent placement, stone basket extraction, and laser lithotripsy in an ASC. Past medical history include hypertension (20 years), diabetes mellitus, (20 years), stroke (10 years ago) with residual symptoms right side weakness, and coronary artery disease with drug-eluting stent placement (10 months ago). She has good exercise tolerance and no angina since coronary stent placement. ECG shows normal sinus rhythm, normal LV function, and LVEF of 69%. Her medications included dual antiplatelet therapy (aspirin + clopidogrel), metoprolol 50 mg OD, lisinopril 20 mg OD, insulin (long-acting and ultra-short acting), and sublingual nitroglycerin 0.4 mg, prn. Is she suitable for ambulatory surgery?

INTRODUCTION

Ambulatory surgery accounts for about 65-70% of all elective surgical procedures performed in the United States[1]. Improvements in surgical and anesthetic techniques as well as modifications in postoperative care have further increased the number of procedures being performed on an outpatient basis. In fact, surgical procedures (e.g., total knee arthroplasty) and patient populations that were once considered inappropriate are increasingly being done in an outpatient setting[2]. Given the changing pattern of health care reimbursement, the expansion of ambulatory surgery is likely to continue. However, there is an uncertainty amongst anesthesiologists, who must determine patient suitability for ambulatory surgery.

For day surgery to be safe and efficient, careful selection of patients and procedures is crucial[3]. Clearly, identifying suitability for an ambulatory procedure is a dynamic process that depends on a complex interplay between surgical procedure, patient characteristics, expected anesthetic technique (e.g., local/regional vs. general anesthesia), and social factors, as well as the ambulatory setting, which will influence the ability to manage complex patients based upon the availabilities of personnel and equipment (Table 1). Although it may be difficult to quantify, appropriateness of patient selection may also depend on the experience and skill of the surgeon and the anesthesiologist. Therefore, attempts to address individual factors without consideration of others is fraught with flaws.

Table 1- Risk Factors in a child with URI:

Surgical procedure
- Minimal invasiveness
- Moderate duration
- Minimal blood loss not requiring blood transfusion
- No specialized postoperative care required
- No need for postoperative parenteral therapy
- Postoperative pain manageable at home

Patient characteristics
- Stable and well controlled coexisting medical conditions
- Disease unlikely to be adversely affected by surgery

Social factors
- Responsible adult escort and availability of a responsible caregiver
- Patient understands instructions
- Reasonable access to a telephone
- Reasonable access to healthcare
- Able to return to hospital within reasonable time frame
- Not expected to care for children or perform hazardous tasks

Ambulatory setting
- Office-based
- Free-standing ambulatory surgery center
- Hospital-based ambulatory surgery center
- Short-stay

This article will discuss the current literature that can guide rational selection for ambulatory surgery in high-risk adults patients.

Table 2: Postoperative outcomes that can be influence by patient selection

- Mortality
- Morbidity
  - Respiratory: bronchospasm, laryngospasm, inability to extubate, airway obstruction, respiratory depression, reintubation
  - Cardiac: arrhythmia, hypotension, hypertension, myocardial ischemia/ infarction, heart failure, pulmonary edema
  - Neurological: cerebrovascular event (stroke/transient ischemic attack)
  - Significant blood loss requiring blood transfusion
  - Significant pain, nausea, vomiting
- Cancelation on day of surgery
- Delayed surgical start
- Delayed recovery and discharge home
- Unplanned hospital admission
- Readmission after discharge home

Evidence Assessing Outcome Ambulatory Surgery

It is well recognized that appropriate patient selection would minimize perioperative complications. The outcome measures influenced by patient selection are presented in table 2. Several studies have used large administrative and/ or clinical databases to assess outcome after various types of ambulatory surgical procedures. All studies have reported a low incidence of serious adverse outcomes and death, most likely because traditionally ambulatory surgery involved relatively healthy patients (i.e., American Society of Anesthesiologists

[ASA] physical status 1 and 2) undergoing low-risk surgical procedures[4-11]. Of note, even if the incidence of a certain complication (e.g., postoperative oxygen desaturation) is significantly higher in a certain population or after a certain surgical procedure, it is not of clinical consequence if it does not influence unplanned hospital admission. Thus, the outcome measures of consequence with regards to clinical decision-making include unplanned hospital admission rate, readmission rate, and death.

The limitations of the observational studies include small sample size, as the incidence of complication rate is very low, which leads to their inability to detect clinically meaningful risk factors. Although several studies have attempted to determine the predictors of postoperative morbidity, they provide only an association and not the causation. Furthermore, these retrospective analyses may not always be relevant in the current rapidly changing surgical and anesthetic practice environment. Thus, the literature that could guide optimal patient selection for ambulatory surgery is sparse and of limited quality.

American Society of Anesthesiologists Physical Status

As ambulatory surgery expands, surgical patients with significant preexisting diseases are more likely to present in an outpatient setting. Although the available evidence is limited, there is a general agreement that patients with a high burden of comorbidities, particularly those with poorly stabilized medical conditions are not suitable for ambulatory surgery. For any patient who is not completely healthy, the nature of any preexisting condition, its stability and functional limitation should be evaluated. Also, rather than attributing risk to a specific disease process and considering comorbid conditions in isolation, it is better to consider interactions between the constellation of diseases.

The ASA physical status is an overall marker of perioperative risk. However, one of the criticisms of the ASA physical status scoring is that it has significant inter-rater variability. Despite its inherent subjectivity, the ASA physical status has moderate inter-rater reliability in clinical practice and could be used as a marker of preoperative health status[12]. There is a general agreement that ASA physical status 3 patients (i.e., patients with severe systemic disease or disease from whatever cause) may be considered acceptable candidates for outpatient surgery if their medical conditions are optimized preoperatively. On the other hand, patients with an ASA physical status 4 may not suitable for ambulatory surgery, particularly if the surgical procedure requires administration of general anesthesia.

Elderly

The prevalence of cardiovascular, cerebrovascular, and pulmonary diseases as well as diabetes mellitus increases with age[13]. Therefore, one of the questions commonly posed is: Is there an age limit for ambulatory surgery? Interestingly, even though the risk of intraoperative events such as hypotension, hypertension, and arrhythmias, appears to be higher in the elderly, they are not at an increased risk for postoperative complications. A retrospective review of elderly (>70 years) patients (n=1647) undergoing ambulatory surgery over a two-year period found no increased risk of complications with the overall unanticipated admission rate of 1.6%[14]. Another retrospective study of elderly patients undergoing ambulatory surgery (n=564,267) noted that the overall risk for hospital admission was low; however, patients of advanced age (age >85) as well as a history of hospitalization within the preceding 6 months were at an increased the risk of readmission[15]. Other studies have reported that the age greater than 80 years is an indicator of increased perioperative risk [10].

Retrospective analysis of the ACS-NSQIP database between 2007 and 2010 assessed the safety of ambulatory laparoscopic cholecystectomy in patients greater than 65 years (outpatients, n=7499 [48.9%] and inpatients, n=7799 [51.1%])[16]. Independent predictors of inpatient admission and mortality included congestive heart failure, ASA physical status 4, bleeding disorder, and renal failure requiring dialysis. Also, some procedures may be inappropriate for ambulatory surgery in the elderly such as transurethral resection of bladder tumors, which is associated with high admission rates.

A scoring system for estimating the possibility of unplanned hospital admission after ambulatory surgery has been proposed[17]. This includes one point each for age (>65 years), operating time longer than 120 minutes, cardiac diagnoses, peripheral vascular disease, cerebrovascular disease, malignancy, seropositive findings for HIV, and regional, and two points for general anesthesia. Increasing scores were associated with higher odds of readmission. For scores of 4 or higher, the odds ratio was 31.96, and 2.8% of these patients were discharged to the hospital.

Overall, age alone should not be used to determine suitability for ambulatory surgery. In fact, in comparison to inpatient, outpatient setting seems to reduce the risk of postoperative cognitive impairment[18-20]. Of note, elderly outpatients may require a greater degree of post-discharge supervision and are more likely to have social issues (e.g., elderly or debilitated spouse) that need to be considered. Furthermore, recovery of fine motor skills and cognitive function is slowed with increasing age.

Obesity

Several studies have identified obesity, which is associated with an increased prevalence of comorbidities, as a risk factor for perioperative complications after ambulatory surgery[9-10]. Thus, one of the clinical questions posed with respect to selection of obese patients for ambulatory surgery is: Is there is a weight (or BMI) limit above which ambulatory surgery is not appropriate?

A propensity-matched analysis of the 2006 National Survey of Ambulatory Surgery database evaluated the overall characteristics and perioperative outcomes in morbidly obese and non-obese patients undergoing ambulatory surgery in the United States[21]. This study found that the prevalence of ambulatory surgery in the morbidly obese was low (0.32%). The morbidly obese were significantly younger but had a higher burden of comorbidities, were more likely to undergo the procedure in hospital based outpatient facilities (80.1% vs. 56.5%), and had significantly shorter procedures than the non-obese (average 28 vs. 42 min). The incidences of postoperative hypertension, hypotension, hypoxia, cancellation of surgery, and unplanned hospital admissions did not differ significantly

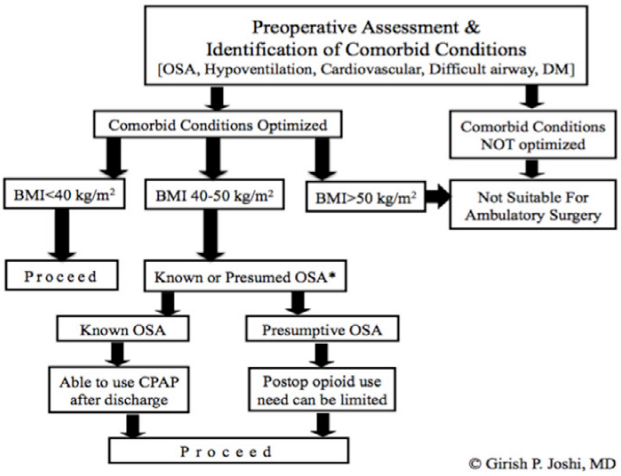

Figure 1: Selection of a patient with morbid obesity and/or obstructive sleep apnea for ambulatory surgery. From Joshi GP, et al: Anesth Analg 2012; 115: 1060-8 and Joshi GP, et al: Anesth Analg 2013; 117: 1082-91.

between groups. Similarly, adjusted rates of delayed discharge were similar in morbidly obese and non-obese patients.

A systematic review revealed that BMI alone did not influence perioperative complications or unplanned admission after ambulatory surgery[22]. Although all the studies included in this systematic review were observational, they were representative of broad clinical practice and included both bariatric and non-bariatric surgical procedures. This systematic review revealed that there was a conservative approach to patient selection for non-bariatric surgical procedures, as the average BMI was only 30 kg/m^2. In contrast the patients undergoing bariatric surgery had a BMI of around 40 kg/m^2, which is known to have a higher burden of comorbid conditions including obstructive sleep apnea. However, the bariatric surgical population had rigorous preoperative evaluation and optimization of comorbid conditions. It was concluded that weight or BMI should not be the sole determinant of patient selection for ambulatory surgery (Fig 1); however, patients with BMI <40 kg/m2 may be suitable for ambulatory surgery assuming that their comorbid conditions, if any, are optimized[22]. Also, it is necessary to consider the presence of sleep disordered breathing (i.e., OSA and obesity-related hypoventilation syndrome), as it has been associated with increased perioperative complications[23]. The super obese (i.e., BMI >50 kg/m^2) should be chosen carefully as they have higher incidence of perioperative complications. For patients with BMI between 40 and 50 kg/m^2, thorough preoperative assessment is necessary to identify obesity-related comorbid conditions (e.g., OSA, obesity-related hypoventilation syndrome, and pulmonary hypertension, as well as resistant hypertension, coronary artery disease, and cardiac failure).

Obstructive Sleep Apnea

It is well documented that patients with OSA are at high risk of perioperative complication[23]. Therefore, suitability of ambulatory surgery in patients with known or suspected OSA remains controversial. Can a patient with known or presumed (clinical) diagnosis of OSA undergo ambulatory surgery?

The ASA recently published updated guidelines regarding perioperative management of OSA patients, including selection for ambulatory surgery[24]. Of note, the previous recommendation that ambulatory surgery is not recommended in OSA patients undergoing airway surgery or upper abdominal surgery has been eliminated[24]. The ASA guidelines also propose a scoring system, based on the severity of OSA, the invasiveness of the surgery, the type of anesthetic technique, and the need for postoperative opioids, that may be used to estimate whether an OSA patient is at increased risk of perioperative complications, and thus determine the suitability for ambulatory surgery. However, clinical utility of this scoring system is questionable, as it has not yet been validated.

A systematic review of published literature assessing perioperative complications in patients with OSA undergoing ambulatory surgery revealed that OSA patients with inadequately treated co-morbid conditions are not suitable for ambulatory surgery[25]. Based upon this systematic review, the Society for Ambulatory Anesthesia (SAMBA) consensus statement recommends that patients with a known diagnosis of OSA, who are typically prescribed positive airway pressure [PAP] therapy, may be considered for ambulatory surgery if their comorbid medical conditions are optimized and they are able to use a PAP device in the postoperative period (Fig 1). It appears that postoperative PAP therapy may be protective against opioid-induced respiratory complications. On the other hand, patients who are unable or unwilling to use PAP device after discharge may not be appropriate for ambulatory surgery. Patients with a presumed diagnosis of OSA, based on screening tools such as the STOP-Bang questionnaire, can be considered for ambulatory surgery if their comorbid conditions are optimized and if postoperative pain relief can be provided predominantly with non-opioid analgesic techniques. It is also recommended that a screening tool be incorporated in a routine preoperative evaluation. The STOP-Bang questionnaire is simple to use; however, it is recommended that a higher 'cut-off' (e.g., ≥ 5 or 6 positive indicators) should be used to determine presumption of OSA, rather than the original suggestion of a 'cut-off' of ≥3.[25-27] Of note, the SAMBA consensus statement did not provide any guidance for OSA patients undergoing upper airway surgery due to limited evidence[25]. However, there is some recent evidence suggesting that airway surgery in this patient population can be performed in an ambulatory setting with complication rates similar to the inpatient population[28-31]. A recent systematic review of 18 publications with 2160 patients assessed postoperative complication rates after OSA surgery performed on same day basis[30]. There were no deaths or major catastrophic events. The overall incidence of any adverse event was 5.3%, with the respiratory-related events rate of less than 1.5%. Most of the respiratory events were related to oxygen desaturations, which were not clinically significant. Exclusion of oxygen desaturation significantly reduced the overall adverse event rates. All the adverse events were related to the surgical procedure and not specifically to OSA. The re-admission rate was only 0.4%. The author concluded that OSA surgery performed on outpatient basis is generally safe and routine hospital admission is not necessary, except for patients undergoing tongue base surgery, those with a higher preoperative apnea/hypopnea index, or those with high postoperative opioid requirements. Other studies have also reported that most serious airway complications occur early

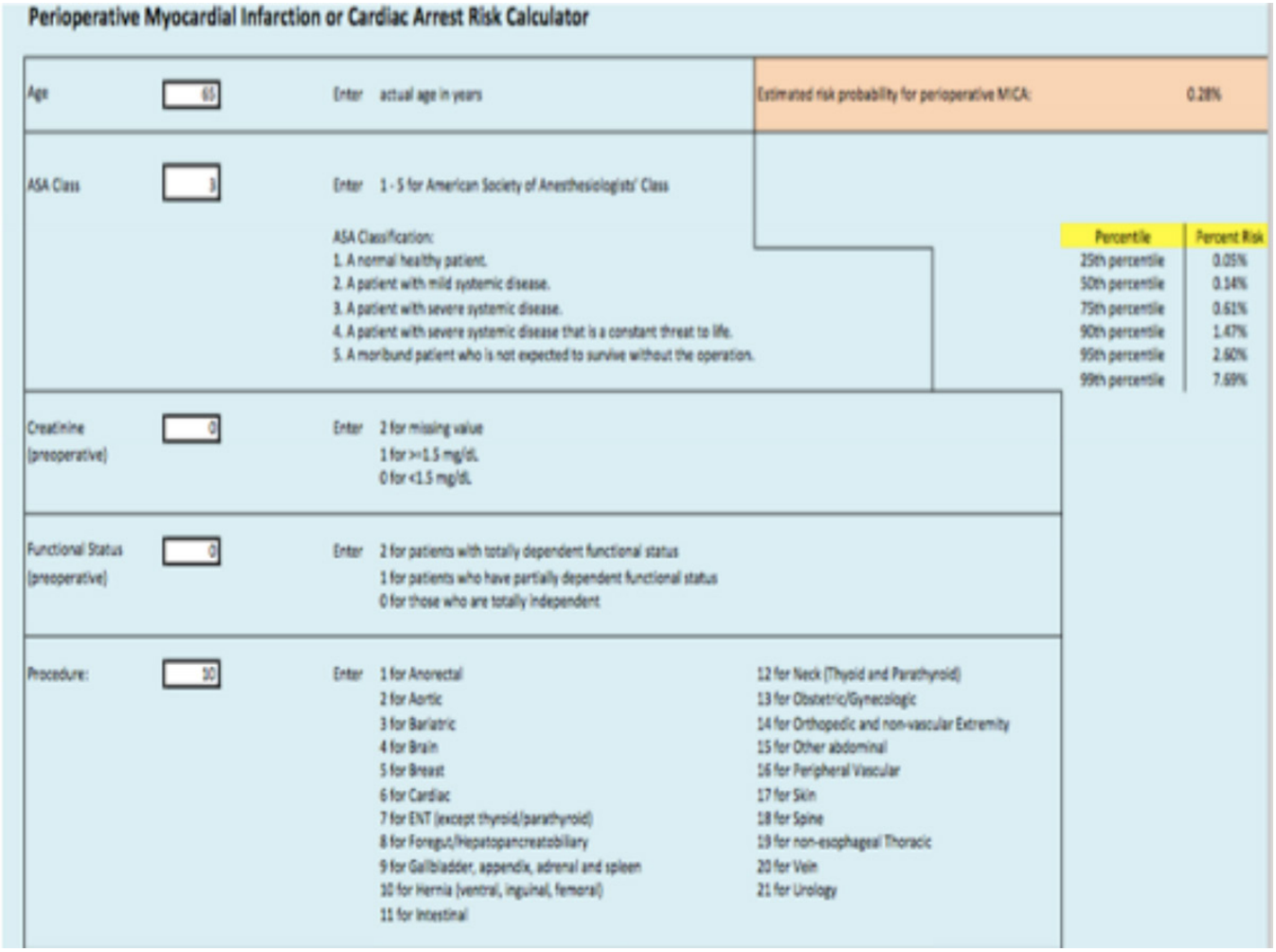

Figure 2: Surgical risk calculator for assessing the risk of perioperative myocardial infarction and cardiac arrest. From Rao A, et al: Am Coll Surg 2013; 217: 1038-48.

after surgery (i.e., within 2 to 3 hours postoperatively)[31]. Potential postoperative complications include airway obstruction, post-obstructive pulmonary edema, and cardiac arrhythmia.

Diabetes Mellitus

Insulin dependent diabetics are at increased risk for perioperative complications such as cardiac, respiratory, and surgical site infections. Although patients with diabetes mellitus often have several comorbidities, it does not appear to be an independent predictor of complication rate after ambulatory surgery. Nevertheless, it is necessary that the surgical facilities caring for this patient population have the necessary equipment to monitor blood glucose levels.

The Society For Ambulatory Anesthesia (SAMBA) has published a consensus statement on perioperative blood glucose management[32], which provides some guidance to address the question: Is there a preoperative blood glucose level (BGL) above which one should postpone elective surgery? Although there is insufficient evidence to specifically recommend a 'cut-off' BGL above which elective ambulatory surgery should be postponed, it may be acceptable to proceed with surgery in patients with preoperative hyperglycemia but with adequate long-term glycemic control, barring any significant complications of hyperglycemia such as ketoacidosis and hyperosmotic states. In patients with chronically poorly controlled diabetes mellitus, the decision to proceed with ambulatory surgery should be made in conjunction with the surgeon and take into account patient comorbidities and the risks of surgical complications.

Cardiac Disease

Due to advances in medical and interventional cardiac care, patients with cardiac disease (e.g., hypertension, coronary artery disease [CAD], arrhythmia (e.g., atrial fibrillation), valvular heart disease, congestive heart failure [CHF], cardiomyopathy, cardiac implantable electronic devices [CIED], coronary artery stents, and congenital heart disease) are increasingly presenting for ambulatory surgery.

Individuals at high risk for perioperative cardiac events, including brittle or poorly controlled hypertension, unstable or severe angina (Canadian class III or IV), recent MI, non-compensated heart failure, symptomatic arrhythmias (high-grade atrioventricular block, supraventricular arrhythmias with uncontrolled ventricular rate, symptomatic ventricular arrhythmias), and significant valvular heart diseases (severe aortic or mitral valve stenosis) may not be suitable for procedures in an ambulatory setting[33].

With technological advances in the management of acute MI, elective surgical procedures may be considered at 30 days post-MI, depending on the patient's symptoms and functional status[34]. Interestingly, patients with CHF and atrial fibrillation (AF) may be at a higher risk of perioperative complications

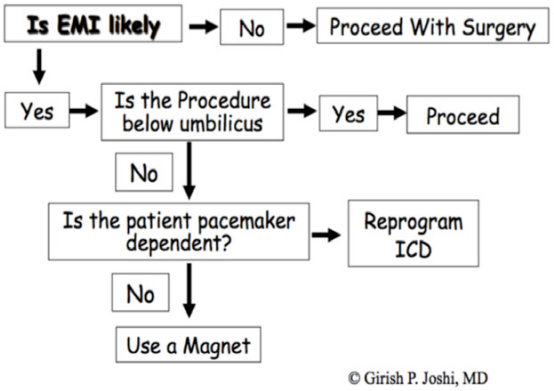

Figure 3: Preoperative considerations in a patient with implantable cardioverter defibrillator. Based on Crosslet GH, et al: Heart Rhythm 2011; 8: 1114-54.

than those with CAD[34]. Several studies have reported an increased incidence of perioperative morbidity and mortality in patients with new onset AF.[35,36] Symptoms associated with AF include fatigue, dizziness, lightheadedness, syncope, palpitations, chest pain or tightness, and shortness of breath. Overall, patients with symptomatic new onset AF may not be suitable for ambulatory surgery.

Most patients with aortic stenosis remain asymptomatic until fifth decade. Once symptomatic (angina pectoris, dyspnea on exertion, or syncope), life expectancy declines with survival limited to approximately 5 years after the presentation of angina and 2 years after the onset of CHF. Patients with hemodynamically significant or symptomatic aortic stenosis may not be appropriate candidates for ambulatory surgery.

Typically, ambulatory surgery carries a low risk of perioperative cardiac complications (defined by a cardiac risk of <1%). The risk of perioperative myocardial infarction or cardiac arrest (MICA) can be calculated by using a cardiac risk calculator (http://www.surgicalriskcalculator.com), derived from the ACS-NSQIP database (Fig 2.). It incorporates patient variables (i.e., age, ASA physical status, functional status, and preoperative serum creatinine) and surgical procedur[37-39]. The predictive performance of this cardiac risk calculator is reported to be superior to that of the Revised Cardiac Risk Index (RCRI), which includes variables such as diabetes mellitus requiring insulin, creatinine ≥2 mg/dL, history of cerebrovascular accident or transient ischemic attack, ischemic heart disease and CHF[40,41]. The presence of ≤2 clinical risk factors is considered at low risk of MACE[40]. Patients at an elevated risk should be assessed for functional status, and those with a functional status of <4 METs or in whom functional capacity cannot be assessed should be considered for pharmacologic stress testing, if it will impact perioperative decision making or care[33].

Patients with CIED may be at risk of perioperative arrhythmia and asystole. Also, in the case of implantable cardioverter defibrillators (ICD) there is a concern that electromagnetic interference may be misinterpreted as an arrhythmia leading to inappropriate shock. The recommendations of the Heart Rhythm Society jointly developed with the ASA, in collaboration with the American College of Cardiology (ACC), the American Heart Association (AHA), and the Society of Thoracic Surgeons (STS) provide excellent guidance for the management of patients with CIED[33,42]. Overall, patients with CIED may safely undergo ambulatory surgery assuming that appropriate equipment and support is readily available (Fig. 3). However, the controversy in management of patients with CIED it related to the use of magnet to disable the ICD and the need for reprogramming (i.e., suspend ICD and pacemaker function), which requires an expert (e.g., a cardiologist, electrophysiology nurse, or device representative) and who may not be always available. Patients with cardiac implantable electronic devices may undergo ambulatory surgery assuming that appropriate support is readily available.

Another challenging group of patients include those with coronary artery stents. The controversy in this patient population surrounds the need to continue the dual antiplatelet therapy to prevent coronary artery thrombosis. It is recommended that patients with acute percutaneous cardiac intervention (PCI) or bare metal coronary stents (BMS) should have their elective surgery delayed for 30 days, while those with drug eluting stents (DES) should have their elective surgery delayed for 365 days[33]. However, controversy surrounds regarding scheduling of patients with newer (second and third generation) DES in whom the dual antiplatelet therapy is maintained for around 6 months[43]. Recent data suggests that elective surgery performed within 6 months of placement of new generation DES is safer than that with BMS and old generation DES[43,44]. Overall, elective surgery should be postponed until the patient is on dual antiplatelet therapy. If necessary, consultation with the patient's cardiologist and the surgeon is recommended to address issues such as timing of surgery, management of anticoagulation, and other potential risk reduction strategies. Because urgent PCI is the best management for acute perioperative stent thrombosis, access to interventional cardiology should be considered in the selection criteria for higher risk patients seeking ambulatory surgery.

SUMMARY

As older and sicker patients undergo more complex surgical procedures in an ambulatory setting, patient selection has become the cornerstone of safe and efficient perioperative care. Developing and implementing protocols (or clinical pathways) for patient selection is the best way to improve perioperative outcome. This requires a multidisciplinary approach in which the anesthesiologist should take a lead in collaborating with the surgeons and the perioperative nurses. Rather than considering the factors in isolation, the interaction of any disease(s) with the planned surgical procedure should also be considered.

The first step in determining appropriate patient selection includes preoperative assessment and identification of any comorbid conditions, which should be optimized to minimize risks. For any patient who is not completely healthy, the nature of any preexisting condition, its stability and functional limitation should be evaluated. The social situation should be evaluated to determine whether the patient has help at home for postoperative care. Education of the patients and their caregivers regarding the need for increased vigilance after discharge home is critical[45]. Outpatients should be capable of understanding instructions for pre- and postoperative care,

and should be accompanied home by a responsible escort. Someone should also be available to care for the patient during the first night after surgery and be able to assist them in obtaining emergency medical care if needed.

The anesthetic technique chosen should provide optimal intraoperative conditions, while ensuring a rapid return of consciousness and protective reflexes upon completion of the operation, minimal residual sedative effects (so-called "hangover" effect), little impairment of postoperative cognitive function, and the absence of side effects during the early recovery period. A pragmatic question to ask is: Will postoperative hospitalization influence patient care or perioperative outcome? If no improvement would be achieved, then the patient should undergo the procedure on an ambulatory basis. In the future, as more patients and surgical procedures are moved from inpatient facilities to outpatient facilities, it will be appropriate to develop exclusion criteria, rather than inclusion criteria, for patients that are not candidates for ambulatory surgery.

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Value-Based Anesthesia Care: Practice Evidence Reversal and Choosing Wisely Campaign

Davy Cheng, MD, MSc, FRCPC, FCAHS, CCPE
Distinguished University Professor & Chair / Chief, Department of Anesthesia & Perioperative Medicine, Professor, Division of Critical Care Medicine, Department of Medicine, Chair, Evidence-based Perioperative Clinical Outcomes Research (EPiCOR), Western University, London, Ontario, Canada

OBJECTIVES:

i) to gain knowledge in value-Based practice for quality outcomes and cost-effectiveness of care

ii) to discuss the current clinical practice reversal in anesthesia and perioperative medicine

iii) to apply Choosing Wisely Campaign and practice reversal with clinical examples in anesthesia, perioperative medicine, transfusion and critical care medicine.

Choosing Wisely Campaign:

It's time to seriously take stock of the cumulative research and evidence base in anesthesia and perioperative medicine, and to reflect on whether research efforts have adequately met the needs of contemporary practice, and can sustain future technological and procedural progress in the field. Existing evidence base remains uncoordinated, with many unrecognized hits and misses, and with significant redundancy and waste. Evidence derived from valid and relevant clinical trials is the life-blood of progress for anesthesia and perioperative medicine. Yet, the results of our ongoing empirical study of the progression of clinical trials in anesthesia and perioperative medicine reveals an urgent unmet need for a better approach toward definitive incremental advances in knowledge - rather than continuously repeating studies that have already been done or that answer the 'wrong' questions.

This lecture will provide a comprehensive overview of the current state of the evidence base in anesthesia and perioperative medicine, and will place it in comparative context with other areas of medicine, where science is also lacking. Lastly, we will explore opportunities and strategies for collective, collaborative and transparent improvement across the field of anesthesia and perioperative medicine, and where we should focus to get best "bang for our buck" in the context of global themes of progress in medicine. Better research (improved validity, importance, and 'translatable' research) and improved efficiency in achieving knowledge translation and evidence-informed practice.

Choosing Wisely Campaign is a physician led initiative to reduce overuse and waste in the US healthcare system. It was launched in 2009 by the National Physicians Alliance and was funded by the American Board of Internal Medicine. The current guidelines and practices in choosing wisely campaign in anesthesia and critical care medicine from the American Society of Anesthesiologists (ASA), Canadian Anesthesiologists' Society (CAS) and Society of Critical Care Medicine (SCCM) will be reviewed and discussed. It is important to understand in order for a successful program to reduce wasteful clinical practices, we must develop tools and strategies to make it easier for clinicians to implement the Choosing Wisely recommendations.

Examples for CXR and Blood Transfusion in Anesthesia and Critical Care Medicine:

Routine Chest Radiography

Don't order routine chest X-rays in critically-ill patients, except when specifically indicated for placement of endotracheal or nasogastric/orogastric tubes, central vein catheters, Swan-Ganz catheters, or any other life-support item, or when a change in the patient's clinical condition requires information from a CXR that will inform a specific decision.

Chest X-rays (CXRs) are not indicated for routine assessment of critically-ill patients except when indicated for specific procedures (endotracheal tube, NG/OG tube, central vein catheter, Swan-Ganz catheter, or other life-supporting item that requires verification post-placement), or to provide information for a specific query related to a change in patient's clinical condition IF the information will likely impact a specific decision related to diagnosis or treatment. In the absence of specific indications, routine CXRs yield many false positives and few meaningful diagnoses, and are more likely to be harmful than helpful. CXRs should be reserved for specifically-defined reasons in situations where the results will be used to change the course of patient care.

Discussion

Evidence Grade: Moderate

Clinical Impact:

- RCTs and observational studies routine CXR does not improve outcomes compared with on-demand CXR. Furthermore, observational studies suggest the diagnostic yield of daily CXR is low in ICU patients, with many false positives spurring unnecessary intervention that did not improve outcomes.

- Meta-analysis of randomized and observational studies show that eliminating daily routine CXR vs on-demand CXR did not affect hospital or ICU mortality (OR 1.02 [95% CI: 0.89, 1.17] and OR 0.92 [95% CI: 0.76, 1.11], respectively), ICU LOS (WMD = 0.19 days; 95% CI: -0.13, 0.51; P = .25), hospital LOS (WMD = -0.29 days; 95% CI: -0.71, 0.13), and ventilator days (WMD = 0.33 days [95% CI: -0.12, 0.78;]). Regression analyses failed to identify any subgroup in which performing daily routine chest radiography was beneficial.

Extent of overuse: High
Amenable to change: Highly Amenable
Cost Impact: Potential for cost savings

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RBC Transfusions

Don't transfuse red blood cells in hemodynamically stable, non-bleeding ICU patients with a hemoglobin concentration greater than 70 g/L.

Unnecessary transfusion of red blood cells (RBCs) is more harmful than helpful, and furthermore wastes a limited resource which should be reserved for life-saving situations. Transfusing RBCs at a threshold higher than 70 g/L does not improve survival in ICU patients, and is associated with fewer complications and reduced costs. Less conservative RBC transfusion thresholds should be reserved for the following patient groups (when fluid management and other interventions remain insufficient): perioperative patients, hemodynamically unstable patients, actively bleeding patients.

Discussion:
Evidence Grade: High
Clinical Impact:

- RCTs suggest threshold of 70 g/L results in similar or lower mortality compared with higher thresholds
- Meta-analysis of RCTs suggest that mortality may be reduced with RBC threshold of 70 g/L compared with higher thresholds.
- Other complications, including stroke and infections, may be reduced with a lower threshold.
- Overall, the evidence suggests reduced harms, and no specific increased risks, with a threshold of 70 g/L.

Extent of overuse: High
Amenable to change: Highly Amenable
Cost Impact: Potential for cost savings

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RECOMMENDED READING

Value and evidence-based in Anesthesia and Perioperative Medicine:

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Regional Anesthesia in Improving Outcomes

Colin John Lindsay McCartney, MBChB, PhD, FRCA, FCARCSI, FRCPC
Professor and Chair of Anesthesiology and Pain Medicine, University of Ottawa, Ontario, Canada

Since the discovery of cocaine medical practitioners have recognized the profound benefits that regional anesthesia can provide for patient care. Significant benefits including pain relief[1] together with a reduction in other adverse effects have led to a dedicated use of regional techniques in many centres around the world over the last 100 years.[2]

In recent decades many studies of the highest quality have demonstrated the perioperative benefits of regional anesthesia on improved pain control (both acute and chronic), reduction in nausea and vomiting, improved mobility and improved organ function.[3]

Recent years have seen the development of methods to further increase efficacy and safety of regional anesthesia and an increased variety of peripheral nerve and infiltration techniques that give a "dizzying" array of possibilities for use in practice. Traditional methods such as the supraclavicular brachial plexus block have seen a resurgence in popularity thanks to the use of ultrasound and newer infiltration methods such as the tranversalis plane (TAP) block and PEC techniques are in high demand in many regional anesthesia workshops across the world.

At the same time justification for the use of regional techniques is becoming increasingly demanding. Minimally invasive surgical techniques and local infiltration methods have vastly improved pain control and early mobility without the need for separate regional anesthesia methods. In addition, public and private health care systems are carefully refining techniques to justify the value of existing and new interventions.

The Institute for Healthcare Improvement (IHI) introduced their Triple Aim of improved population health, patient experience and lower per capita cost in 2008 and since that time this framework has been used as an integral component in a number of health systems around the world including systems in the United States, United Kingdom and Canada to guide advances in care.[4] Surgical populations are a major target for improving value in healthcare because surgically treatable diseases are responsible for approximately 33% of deaths, 28% of disability-adjusted loss in life-years and 23% of years lived with disability.[5] Regional anesthesia techniques have major potential for having a positive impact on triple aim outcomes and this paper (and associated lecture) will summarize the following:

1. Why regional anesthesia has positive benefits on triple aim outcomes?
2. Identify those populations who have most to benefit from regional anesthesia according to the triple aim.
3. Draw conclusions to guide current practice and future research regarding best practice.

Why regional anesthesia has positive benefits on triple aim outcomes?

Regional anesthesia has always demonstrated profound benefits both on pain relief and reduction in need for other systemic analgesic drugs. Patients greatly value good postoperative pain control[6] but the reduction in other systemic drugs also reduces nausea, bowel ileus and dizziness. This in turn can improve postoperative mobility and improve sleep. Although better pain control and reduced side effects would seem to be of sufficient benefit in isolation improved early pain control has been shown in selected populations to also reduce length of stay and chronic pain after surgery.[7,8] Recent data from large patient populations indicates that regional anesthesia can also reduce major morbidity and mortality compared to those patients who have general anesthesia.[9] Patients value good quality pain control and reduce of associated adverse effects and this impact on patient experience should not be undervalued.[10]

Mechanisms of improvement in patient outcomes remain unclear but several physiological mechanisms may explain why regional anesthesia has these effects. Reductions in sympathetic drive, decreased surgical stress response and improved cardiovascular responses including reduced myocardial afterload reduce risk of adverse cardiovascular events. Greater pain control facilitates ability to breathe and cough and reduces incidence of respiratory complications. Better pain control may improve sleep and facilitate early rehabilitation.

Table: Potential Impact of Regional Anesthesia Techniques on the IHI Triple Aim

Early Outcomes	Intermediate Outcomes	Triple Aim Outcomes
Decreased Pain	Decreased LOS	Improved Population Health
Decreased PONV	Decreased readmission	Better Patient Experience
Improved Mobility	Decreased complications	Lower Cost
Improved Organ Function		

Who are the populations with most to benefit from regional anesthesia?

Many proponents could make an argument for the use of local anesthetic techniques in all surgical procedures. However rational use of regional anesthesia is important to balance the cost and time that these procedures necessitate to provide high quality care. Surgical infiltration should be used in even the most minor of surgical cases and regional anesthesia has demonstrated benefits on early pain control, avoidance of side effects and discharge in many ambulatory surgical procedures.[11] Recent evidence from large databases indicate that patients having major orthopedic surgery have significantly reduced incidence of major morbidity and mortality with the use of neuraxial techniques compared to

general anesthesia.[9] Use of peripheral nerve blocks can also have major impact on morbidity. Perhaps the most surprising aspect is that the use of neuraxial techniques remains disappointingly low in many areas of the world including the United States.[12]

Conversely, the use of regional anesthesia techniques in major thoracic and abdominal surgery lacks high quality evidence with regard to triple aim outcomes.[13] In particular, emergency surgery has not been well examined. Further evidence identifying the benefit of regional anesthesia on the triple aim in these populations is necessary before further guidance can be given. The use of newer infiltration methods such as the transversalis plane block and PECS methods require further evaluation before they can replace existing methods such as epidural and paravertebral techniques.

Conclusions and Future Directions

Regional anesthesia remains a powerful technique for improving early pain control and reducing adverse effects after many types of ambulatory and inpatient surgery. Rational use of regional techniques is important to justify the extra time and expense that is often necessary to provide high quality care. However, for many types of orthopedic and general/pelvic surgery these improvements can be provided in an organized environment. Recent evidence indicates that use of neuraxial techniques and peripheral nerve blocks can have more profound effects on population health after orthopedic surgery especially in older populations. The use of regional anesthesia should be carefully organized to facilitate use in these populations.

In the future, pragmatic randomized trials examining large numbers of patients will provide further data to examine recent evidence from large databases.[14] Patients should have more input on the types of questions being asked in order to provide answers to questions relevant to patient concerns. Finally, the use of qualitative methods to further examine important areas of the triple aim especially around patient experience may be of benefit.

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Point of Care Ultrasound in Perioperative Care

Vincent WS Chan, MD, FRCPC, FRCA
Professor, Department of Anesthesia, University of Toronto

James A. DiNardo, MD, FAAP
Professor of Anaesthesia, Harvard Medical School, Chief, Division of Cardiac Anesthesia

Francis X. McGowan, Jr., MD
Chair in Cardiac Anesthesia, Boston Children's Hospital

While use of hand held, point of care ultrasound (POCUS) is commonly employed by anesthesiologists in the conduct of regional anesthesia its use in assessment of cardiac and pulmonary pathology is substantially less common than among intensive care and emergency medicine physicians. During this lecture the audience will be shown how POCUS can be utilized to perform focused transthoracic echocardiographic (TTE) and lung ultrasound examinations. Several features characterize POCUS as follows:

- Exam is for a well-defined purpose linked to improving patient outcomes
- Exam is focused and goal-directed
- Exam findings are easily recognizable
- The exam is easily learned
- Exam is quickly performed
- Exam is performed at the patient's bedside

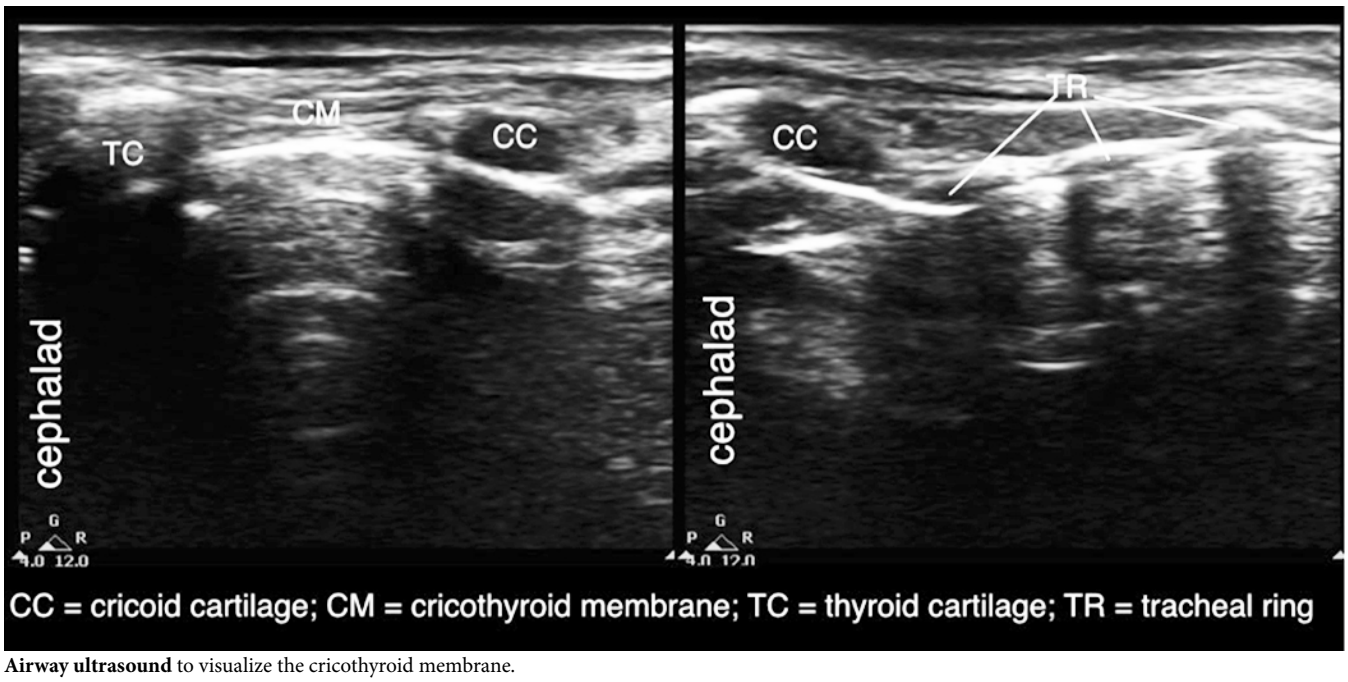
Airway and Diaphragm Ultrasound

Superficial airway structures are easily palpable except in patients with poorly defined neck anatomy. Deep airway structures e.g., epiglottis, base of the tongue, vocal cords can be visualized by ultrasound. Preliminary studies show promising role of ultrasound for airway assessment e.g., predicting difficult intubation (Hui), vocal cord swelling and post extubation stridor (Mikaeili), identification of esophageal vs. tracheal intubation in out of hospital setting (Muslu) (Ramsingh) (Zadel) and evaluation of laryngeal mask airway position (Kim). Ultrasound can also aid intervention e.g., cricothyrotomy in subjects with poorly defined neck anatomy (Siddiqui) and percutaneous dilatational tracheostomy (Dinh).

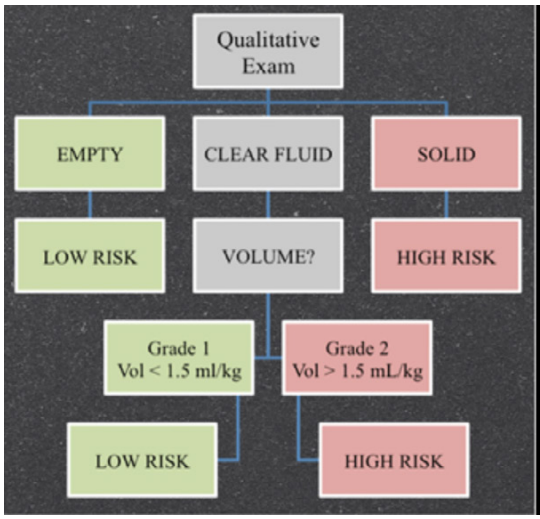
Ultrasound can assess diaphragmatic excursion qualitatively and quantitatively (using M mode) during quiet breathing, deep breathing, and sniffing (Matamis) (Sarwal). It can also assess diaphragm thickness as a measure of atrophy and weakness in critical care patients during mechanical ventilation (Francis). Ultrasound is being used increasingly by regional anesthesiologists to differentiate hemidiaphragmatic hemiparesis due to phrenic nerve block from pneumothorax as the cause of respiratory distress following interscalene brachial plexus block.

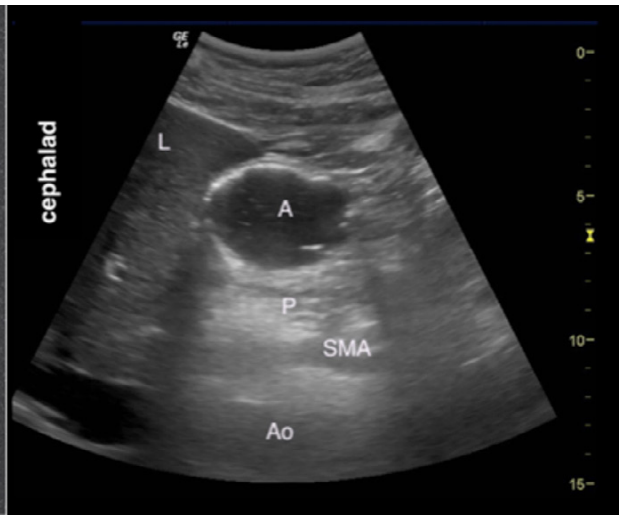
Gastric Ultrasound

Preliminary data show that gastric ultrasound (GUS) can be a useful bedside diagnostic tool to evaluate stomach contents (empty, fluid, thick fluid or solid) and volume (Van de Putte) (Perlas 2016) when NPO (nil per oral) status is questionable or unknown in patients undergoing elective or emergency surgery and parturients prior to cesarean section (Arzola). This type of assessment helps determine pulmonary aspiration risk and guide anesthetic management (see algorithm). Focused GUS evaluation of the gastric antrum (cross sectional measurement) both in the supine and right lateral decubitus positions helps guide the anesthetic management of elective surgical patients who have not



Airway ultrasound to visualize the cricothyroid membrane.



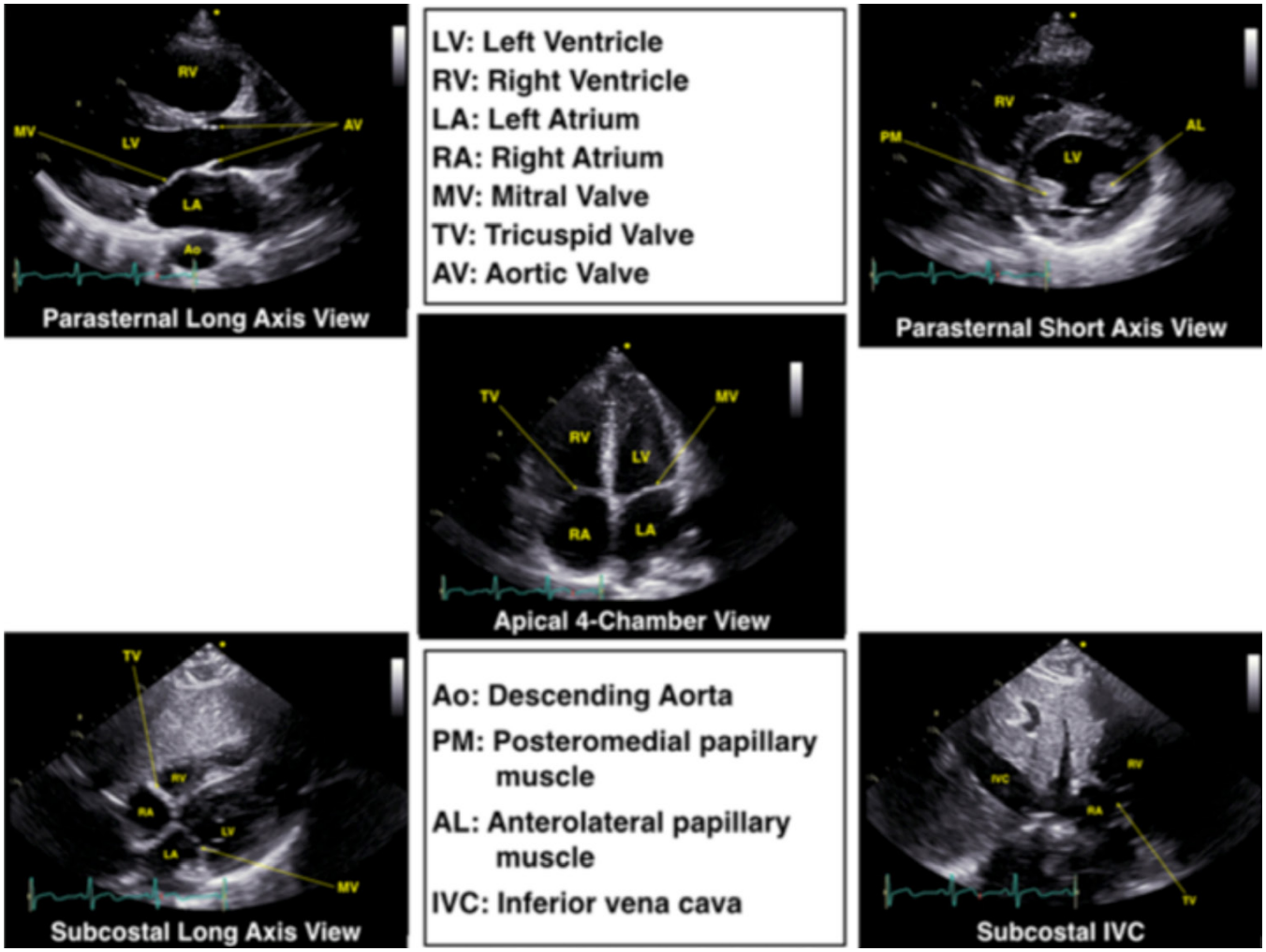


A = gastric antrum (fluid)
Ao = aorta
L = liver
P = pancreas
SMA = superior mesenteric artery

followed fasting instructions (Alakkad). The age dependent gastric volume based on gastric antral cross-sectional area measured in the right lateral decubitus has been determined in adult (Perlas 2013) and pediatric (Spencer) subjects.

Optic Nerve Sheath Diameter (ONSD) Assessment

The optic nerve sheath is contiguous with the dura mater which in turn is contiguous with the subarachnoid space. Raised intracranial pressure (ICP) results in increased optic nerve sheath diameter and papilledema. Bedside ultrasound measurement of ONSD has been found to be a strong predictor of raised ICP in traumatic and non traumatic brain injury (Amini) (Bäuerle). The cut-off value for normal ONSD, measured 3 mm posterior to the globe, ranges from 5.2 to 5.9 mm (a relatively wide interindividual range). There is a good correlation between ONSD and CT scan in ICP detection Ohle)



FoCUS Exam From reference Ursprung E, Oren-Grinberg A Int Anesthesiol Clin 2016; 54:1–21

(Sekhon) and has a relatively high sensitivity for ruling out raised ICP in low-risk and high specificity for ruling in raised ICP in high-risk patients (sensitivity 74–95% and specificity 74–100% to identify ICP >20 mmHg). However, ONSD examination has a false-negative rate of approximately 10% thus interpretation with clinical data and other neuroimaging studies is necessary.

TTE

The focused cardiac ultrasound (FoCUS) exam is an invaluable tool in the assessment of hemodynamic compromise and frank shock because it can rule out or diagnosis tamponade, significant ventricular systolic dysfunction, PE, severe hypovolemic, or major valvular dysfunction. The FoCUS exam utilizes 5 TTE views. The subcostal (subxyphoid) long axis or 4 chamber view is particularly useful because it can be obtained during CPR and in patients with poor parasternal and apical windows due either to body habitus or lung inflation as a consequence of the requirement for mechanical ventilation.

Lung Ultrasound

The bedside lung ultrasound in emergency (BLUE) exam is a valuable tool in assessment of pneumothorax, pleural effusions, pulmonary edema, ARDS, and atelectasis/consolidation. The BLUE exam utilizes 6 lung US windows. Unlike the FoCUS exam the BLUE exam requires familiarity with use of M-mode US. We will focus on the diagnostic significance of a number of lung ultrasound findings:

- Normal findings
  - Bat sign
  - Pleural line
  - Lung sliding
  - Seashore sign
  - A lines
- Pleural effusion
  - Quad sign
  - Sinusoidal sign
- Pneumothorax
  - Barcode sign
  - Lung point
  - A lines
  - Loss of B lines
- Interstitial syndrome (pulmonary edema and ARDS)
  - B lines
- Consolidation
  - Tissue sign
  - Shred sign

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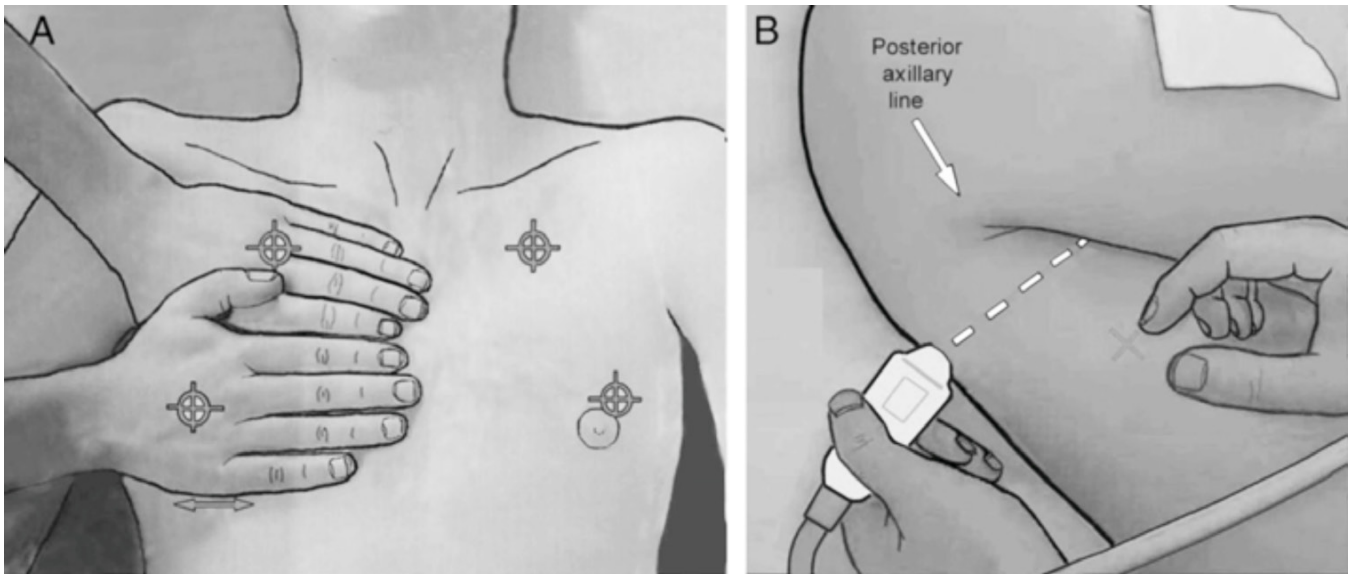

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Excellent resource with WEB based interactive videos covering all aspects of cardiac and lung POCUS exams http://pie.med.utoronto.ca

Hot Topics in Cardiac Anesthesia 2016

James Ramsay, MD
Professor of Anesthesia, Medical Director, CT Surgery ICU, Moffitt Hospital,
University of California, San Francisco, California

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

(1) Explain the potential anesthetic options and implications of interventional rather than surgical valvular interventions
(2) Apply new cardiovascular pharmacologic strategies to support cardiac function and vascular tone
(3) Compare and evaluate anesthetic implications related to placement of new cardiac support devices.

INTRODUCTION

While there have been no new earth-shattering discoveries for the cardiac anesthesiologist in the last year, there are several areas of interest with new information which can affect our practice and care of patients. We continue to see an increasing number of publications related to percutaneous valve replacement, there is a new (to North America) inotropic drug, levosimendan, being studied in the setting of cardiac surgery, and there is at least one new ventricular assist device under study in the United States.

Other topics to be discussed include changes in coagulation management due to the increasing availability of concentrated coagulation factors (prothrombin complex concentrates or "PCCs") and fibrinogen, and approaches to detect and/or reduce the incidence of transient or permanent renal dysfunction seen after cardiac surgery. I will not discuss advances in transesophageal echocardiography (TEE) other than to mention the increasing adoption of real-time 3 –dimensional imaging by our subspecialty. The reader is referred to a recent article addressing the current and future trends for use of TEE in the perioperative setting.[1]

Percutaneous Valve Procedures

Percutaneous aortic valve replacement or "TAVR" is now generally accepted as a viable option for elderly, high risk patients. What is new is an increasing interest in expanding this option into lower risk populations. In April 2016, Leon et al[2] reported on 2032 patients studied at 57 North American centers from 2011-2013 comparing use of the Edwards Sapien XT valve vs surgical valve replacement in patients deemed to be at "intermediate risk" (estimated mortality risk from surgery 4-8% at 30 days) using the Society of Thoracic Surgeons (STS) risk assessment tool. The transfemoral group experienced lower mortality and disabling stroke than with open surgery, while the transapical group was equivalent to surgery. Looking at all patients, the open surgical patients experienced fewer vascular complications and less aortic regurgitation; the percutaneous patients experienced less kidney injury, bleeding and new onset atrial fibrillation.

While the patients were at "intermediate" risk the mean age was 80 years, thus not representing the younger, healthier patients we may see needing aortic valve replacement. On the other hand, similar to studies describing drug-eluting stents for coronary disease where by the time the studies are published cardiologists are using newer, better stents, the valve used in this study has been replaced by a newer model which is expected to provide superior results (eg less paravalvular regurgitation, smaller less traumatic delivery system). It seems inevitable that TAVR delivery systems and valves will continue to improve and thus provide better clinical results, making this procedure more attractive for lower risk patients.

All of the cardiac valves are now candidates for percutaneous replacement, but development of specific devices for specific valves other than the aortic is slow. Due to its complex anatomy and less rigid ring structure with the common pathologies, the mitral valve is a particular challenge. That being said, there are prototypes in development[3]and use of the "mitra-clip" which significantly reduces regurgitation is now widespread. Transcatheter valves can be used to replace bioprosthetic valves in any position ("valve in valve") and with appropriate pathology and anatomical considerations, may be used in right sided locations.

Searching through the Leon et al manuscript[2] and online supplementary data, I found one reference to anesthesia – in the informed consent form, where the patients were told if they underwent the transfemoral valve procedure they may get local or general anesthesia (GA). The main manuscript does not contain the word anesthesia. An international survey published in 2014 suggested approximately 92% of North American transfemoral procedures were done with GA; outside of North America the number was 75%.[4] More recently Mayr et al[5] reviewed 13 non-randomized reports or registries including more than 6,000 patients where approximately half received sedation rather than GA, and the conversion rate to GA varied from less than 2% to about 17%. A single center report from Washington DC this year, where sedation was the "norm" (90% of patients), reported a conversion to GA rate of 12% and overall improved outcomes with sedation.[6] This was not a randomized study and the outcome difference is hard to attribute to the anesthetic technique but provides additional evidence that sedation can be safe and effective; the majority of the patients underwent TEE during the procedures under sedation. In both of these reports the authors recommend the continuous presence of an anesthesia team, ready to induce GA and intubate.

The femoral route for TAVR is the preferred route as most studies have, similar to Leon et al[2] found that the outcomes are generally better. This is also the main route compatible with sedation rather than GA; for the transapical approach GA is required.

Levosimendan

As the first of a class of inotropic drugs termed "calcium sensitizers" levosimendan was developed in 1994, entered clinical practice in 2000, and is now available in more than 50 countries but not the United States.[7] There are a great many published clinical trials in both the medical and surgical setting; unfortunately two large trials done in the USA in the setting of acute heart .[8,9] Many other clinical trials demonstrate acute hemodynamic and outcome benefits; a very large meta-analysis (175 trials) published in 2015 concluded that of all inotropic drugs only levosimendan was associated with a reduced mortality.[10] There is currently a large industry sponsored multicenter trial under way in North America to assess levosimendan (vs placebo) for use in patients with low ejection fraction undergoing cardiac surgery.

Levosimendan binds to troponin C making it more sensitive to calcium ions, thereby increasing contractility o.[7] This is only one of the actions of the drug, however. In addition it promotes opening of the potassium channels of smooth muscle cells, opening of potassium channels on the mitochondria, and it is a selective phosphodiesterase (PDE) III inhibitor. These actions make it a vasodilator and also a potential cardioprotectant. Unlike catecholamines which increase energy demands of the myocardium, levosimendan does not. Also unlike either the short acting catecholamines or longer acting PDE inhibitors such as milrinone, levosimendan's prolonged pharmacologic action appears to be principally from an active metabolite OR-1896, which has an elimination half life of 80 hours in patients with heart failure. The parent drug has a rapid onset of clinical effect but an elimination half life of only 1.5 hours. Levosimendan is given as an infusion over several hours (in the current North American study over 24 hours) with an expected duration of action of days.

Ventricular Assist Devices

The intra-aortic balloon pump (IABP) has been described as a ventricular assist device although it does not actually pump blood; its benefits are improved coronary perfusion pressure with balloon inflation and decreased afterload with balloon deflation. It is used in the interventional setting and perioperatively for acute cardiac failure, most often when failure is caused by acute ischemia. What is new for the IABP is the recent (2012) publication of a large study which failed to find a benefit in the setting of cardiogenic shock due to myocardial infarction, challenging a 5 decade practice.[11] Other recent reviews (eg Cochrane) have come to a similar conclusion, and the strength of recommendation for use of the IABP in this setting has been weakened in both European and American guidelines.[12] Similar to the periprocedural setting, the use of temporary assist devices which actually provide flow is definitely on the increase and becoming as or more likely to be utilized than the IABP although there is at this time no compelling evidence regarding their impact on outcome.

Cardiac anesthesiologists are called upon to provide anesthesia care for surgical placement of durable ventricular assist devices, for care and TEE assistance in guiding or verifying position of cannulae and devices designed for short term use, and for the interventions where devices are replaced, modified, transitioned from temporary to permanent, or "weaned" and removed. With the proliferation and increasing use of these devices, familiarity is essential.

"Short term" Left Ventricular Assist Devices

In North America there are two percutaneous left ventricular devices, the Impella (made by Abiomed) and Tandem Heart (made by CardiacAssist Inc). These devices are usually placed with the patient in the catheterization laboratory using radiologic guidance, and are used to support a patient through an intervention or temporize in the ICU until a more definitive solution can be obtained. The Impella is a miniaturized axial pump mounted on a catheter that traverses the aortic valve, drawing blood from the left ventricle (LV) to the ascending aorta. It is a single cannula device usually placed via the femoral artery, but can also be placed via the axillary/subclavian route. Flows of up to 5 L /min are possible with the largest version of the Impella. A recent study has demonstrated that this device can remain in place for weeks rather than days (approved indication is 6 hours), while a patient may be either recovering from an acute process or be fully evaluated for a definitive therapy such as durable LV assist device (LVAD) or heart transplant.[13] The Tandem Heart requires two cannulations, usually femoral, where a venous catheter is advanced trans-septally to the left atrium to aspirate blood, and an arterial cannula is placed for infusion. The centrifugal pump is extracorporeal.

"Short term" Right Ventricular Assist Devices

Abiomed has developed the Impella RP device, designed for femoral venous insertion, for use on the right side of the heart, with two publications demonstrating benefit in patients both after LVAD placement and in patients with other causes of right heart failure.[14,15] CardiacAssist has a similar solution ("Protek-duo") using a single cannula placed through the right internal jugular vein that aspirates blood from the right atrium and pumps it (via an extracorporeal circuit) into the pulmonary artery.[16] As the pump is extracorporeal an oxygenator may be included in the circuit, providing Veno-venous (VV) ECMO in addition to right heart assist.

Durable Ventricular Assist Devices (VADs)

The world of ventricular assist devices was transformed in the last decade with the introduction of continuous flow pumps and then an exponential increase in use due to the impressive survival. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), a public–private partnership between the National Heart, Lung and Blood Institute (NHLBI), hospitals, and industry, with 158 participating hospitals, publishes an annual report of their registry of LVAD placement in the United States.[17] Currently, with more than 15,000 patients in the registry, this group reports an overall survival with continuous flow devices of 80% at 1 year, and 70% at 2 years. In the United States two devices are currently implanted: the Thoratec Heart Mate II device (approved for both bridge to transplant and destination therapy), and the HeartWare HVAD (approved for bridge to transplant). A third device, the Reliant Heart HeartAssist5, which is an axial flow pump smaller than its predecessors with a number of advanced monitoring features,

is currently undergoing a clinical trial in the US, for the bridge to transplant indication. As indicated in the INTERMACS report, less than 3% of patients between 2012-2014 received a "BIVAD," with significantly worse outcomes as might be expected. Use of the "total artificial heart" is limited to very few centers and comprises less than 1% of all durable ventricular assist device implantations.

Expert TEE imaging to help guide or verify the position of inflow and outflow implantation sites for a VAD, to evaluate for aortic insufficiency, tricuspid insufficiency and the possible presence of a patent foramen ovale (PFO), and to continuously evaluate right heart function after VAD implantation has become a required skill of the cardiac anesthesiologist. As the number and survival of these patients continues to increase, more and more patients are presenting for noncardiac procedures. They are anticoagulated, often present difficulty in measuring blood pressure due to the nonpulsatile flow, and function of their device sis poorly understood by non-cardiac care providers, these patients present anesthetic challenges which are most likely to be referred to the cardiac anesthesiologist.[18]

Extracorporeal Membrane Oxygenation (ECMO)

Similar to the experience with VADs, the application of continuous flow centrifugal (rather than roller) pumps, as well as the incorporation of pump and oxygenator in one portable unit (Maquet Cardiohelp), along with refinements in cannulae including biocompatible coatings, has led to greater viability of multi-day and even multi-week extracorporeal cardiorespiratory support, and an exponential increase in use. Veno-arterial (VA) ECMO which provides respiratory and biventricular support (ie for failure of either or both ventricles) can be instituted urgently in an acute care setting (eg, ER or ICU) via percutaneous or cutdown femoral cannulae and can be life-saving in both acute cardiac and respiratory failure. Cannulation at other access sites and placement of specialized cannulae for VV ECMO (eg, internal jugular Avalon or Protek-duo cannula) is performed surgically in the operating room with TEE and/or fluoroscopic assistance. Inability to separate from cardiopulmonary bypass may lead to initiation of ECMO (either femorally, or with central cannulae) after cardiac surgery.

The Extracorporeal Life Support Organization (ELSO), based in Ann Arbor, MI, is an international consortium which keeps a registry of ECMO in participating centers around the world. The latest report includes almost 300 centers and more than 73,000 patients; overall survival to discharge of adults for respiratory indications is 58% and for cardiac 41%.[19] This organization provides training and other educational resources for participating members as well as a scientific leadership and structure. Publications regarding the assessment for survivability before initiating ECMO, one of the most difficult parts of providing ECMO care, have recently appeared.[20,21]

Prothrombin Complex Concentrate (PCC) and Fibrinogen

One of the most complex, time consuming and controversial activities of the cardiac anesthesiologist is dealing with perioperative coagulation issues, in particular managing postoperative coagulopathy. What is new in recent years has been the introduction of concentrated specific factors derived from human plasma which are convenient, do not require matching to blood type, are reconstituted in a small volume and able to be given rapidly. The products are treated to prevent transmission of infection. Experience with recombinant factor VIIa has shown us that specific procoagulants can be a two-edged sword, as off-label emergent use in the cardiac surgery setting with doses developed for inherited factor deficiency is not without a risk of life threatening thrombosis even though it can clearly bring many bleeding states under control.

The newest agents to become available in the United States are PCCs and fibrinogen; both have been available outside this country for some years. The FDA approved indication of PCCs is urgent reversal of vitamin K antagonist induced coagulopathy; use in the setting of cardiac surgery is "off label." In a similar way, the only approved indication for fibrinogen is treatment of bleeding in the setting of congenital fibrinogen deficiency.

There are no randomized trials comparing the use of PCCs to fresh frozen plasma (FFP) for post-CPB bleeding; two recently published retrospective analyses in patients undergoing pulmonary embolectomy under deep hypothermic arrest[22] and in a general population of cardiac surgery[23] demonstrated reduced chest tube drainage after surgery, but no reduction in transfusion of other blood products. One of these trials found a statistically significant increase in acute kidney injury in patients receiving PCCs;[23] the other found only a numerical (but not statistically significant) difference in the same direction.[22] It is possible the additional volume of FFP vs PCC could have contributed to these findings. While we await carefully performed prospective trials, it is possible to make some general recommendations regarding the use of PCCs as outlined in a recent review.[24] First, there are several products available on the market worldwide, with different factors (3-factor vs 4-factor), different amounts of each factor, and some contain small amounts of heparin. Clinicians must understand the composition of the product(s) available in their institution. Dosing in the setting of vitamin K antagonist induced coagulopathy is based on the international normalized ratio (INR); in the setting of bleeding after surgery in patients who have not received vitamin K antagonists it is likely that lower doses are effective and safer in terms of inducing a prothrombotic state. Bleeding "protocols" after cardiac surgery increasingly rely on point-of-care coagulation testing based on viscoelastic tests of clot formation (thromboelastography or TEG, and ROTEM), a feature of both studies quoted above; experts on perioperative coagulopathy recommend use of these devices to guide administration of either FFP or PCCs.

Similar to PCCs, lyophilized concentrated human fibrinogen (RiaSTAP) may be reconstituted quickly in a small volume (fraction of what is needed with regard to FFP or cryprecipitate). A recent randomized trial reported a significant reduction in bleeding and the need for blood products when fibrinogen, given according to on-CPB fibrinogen activity and guided by viscoelastic clot analysis (ROTEM) was administered after protamine.[25] In an editorial addressing the use of fibrinogen after CPB, Miceli et al[26] caution that while it may be effective, there is little evidence

upon which to base recommendations for clinical use including indications, dosing and frequency are still uncertain and await further clinical trials.

Prevention of Renal Injury and Failure

Acute kidney injury (AKI) and renal failure after cardiac surgery are associated with poor outcome. In a 1998 prospective data collection in patients undergoing myocardial revascularization on CPB, Mora Mangano et al found an incidence of dysfunction (elevated creatinine) of 7.7% and failure requiring dialysis of 1.4%.[27] Patients who needed dialysis had a mortality of 63%, compared to 19% with dysfunction and 0.9% with neither. Many other more recent studies have mirrored these findings, including some in off-CPB surgery, although the incidence of acute injury (but not need for dialysis or effect on long term kidney function) may be lower with this approach.[28] A number of pharmacologic approaches have been taken to try to prevent the occurrence of renal injury, including administration of N-acetylcysteine or bicarbonate infusions perioperatively, and most recently, supplementation of serum albumin. A meta-analysis published in 2011 did not find a benefit of N-acetylcysteine,[29] nor did a meta-analysis published in 2014 looking at sodium bicarbonate.[30]

A recent double-blind study performed in off-CPB surgery showed that administration of albumin before surgery in hypoalbuminemic patients reduces the risk of AKI, but not need for dialysis.[31] Whether or not this was simply a volume effect, or something intrinsic to the albumin molecule is uncertain. In North America the vast majority of revascularization surgery is performed with the use of CPB; similar studies need to be performed in patients undergoing heart surgery with CPB.

A new marker of impeding or early AKI has recently become available in the United States: neutrophil gelatinase-associated lipocalin (NGAL). This marker has received considerable research attention and appears, in many settings, to detect the onset of renal injury before either oliguria or elevated creatinine occur. A recent review and meta-analysis suggests the test is valid in cardiac surgery patients, especially those with normal baseline renal function.[32] The hope is that early detection could facilitate initiation of measures to improve kidney perfusion and possibly limit the degree of injury.

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10 Things You Always Wanted to Know About Pediatric Anesthesia and The 5 Things That Drive Me Nuts!

James A. DiNardo, MD, FAAP
Professor of Anaesthesia, Harvard Medical School, Chief, Division of Cardiac Anesthesia

Francis X. McGowan, Jr., MD
Chair in Cardiac Anesthesia, Boston Children's Hospital

Preoperative Anemia is Neonates is BAD

Neonates have a high incidence of perioperative mortality worldwide[1-5]. In a recent study, the incidences of 24-hour and 30-day mortality in children were respectively 13.3 per 10,000 anesthetics and 41.6 per 10,000 anesthetics, while a higher 30-day postoperative mortality rate of 386.5 per 10,000 was reported in the neonatal population[2]. In another study, postoperative 24-hour and 30-day mortality in children were reported as 0.98 deaths per 10,000 anesthetics while both the 24-hour (168.7 deaths per 10,000 anesthetics) and 30-day (350.4 per 10,000 anesthetics) mortality was substantially higher in neonates[1]. The incidence of postoperative neonatal mortality in US hospitals has never been reported. In addition, while preoperative anemia is a well-established independent risk factor for mortality in adults[6-9], the effect of preoperative anemia on mortality in neonates undergoing non-cardiac surgery has only recently been investigated[10]. The incidence of preoperative neonatal anemia is 32%, the incidence of postoperative in-hospital mortality in neonates is 3.4%. Preoperative anemia (Hct < 40%) is an independent risk factor for postoperative in-hospital mortality in neonates; odds ratio being 2.6. Timely diagnosis, prevention and appropriate treatment of preoperative anemia in neonates might improve outcomes and survival.

Transfusion Volume is an Important Determinant of Morbidity and Mortality in Children

Erythrocyte transfusions are considered by some to be one of the most overused treatments in modern medicine, administered at a cost of billions dollars.[11] Approximately 15 to 25% of children admitted to Pediatric Intensive Care Units (PICU) receive at least one erythrocytes transfusion[12,13], and almost 50% of children with a PICU stay of more than 48 hours will be transfused.[14] Erythrocyte transfusion in infants and children is also reported to occur in the context of some major non-cardiac surgical procedures such as liver transplant (>80%), craniofacial surgery (>60%), and scoliosis surgery (>20%).[15]

While erythrocyte transfusion is an important part of supportive care and can be lifesaving during hemorrhage or in children with severe anemia[16], transfusion of blood can also adversely affect clinical outcomes.[17] Although improvements in hemovigilance have significantly reduced the risk of transfusion-related infections, the reported incidence of serious hazards of transfusion (SHOT) has increased, particularly in infants.[18] Until recently, no study has assessed the relationship between the volume of erythrocytes transfused and outcomes in a large non-cardiac pediatric surgical population. Recently our group demonstrated that erythrocyte transfusion is associated with an increased incidence of 30-day mortality and postoperative infection in children undergoing non-cardiac surgery.[19] Children that received a larger volume of erythrocytes had an increased risk of mortality and postoperative infection with the risk of those adverse outcomes increasing with increasing transfusion volumes above 40 mL/kg.

Co-Existing CHD is TROUBLE

Over the past decades, significant advances have been made in the diagnosis and treatment of children with congenital heart disease (CHD).[20] Although the overall incidence of CHD has remained stable during the last 50 years, the natural history of lesions and the overall survival rate have significantly changed.[21] Advances made in surgical procedures (e.g. cardiac catheterization, systemic-to-pulmonary arterial shunts) and techniques[22,23], in concert with improvements in diagnosis, anesthesia practices, intensive care, and medical treatments have transformed many of these fatal lesions into manageable chronic conditions.[24]

As life expectancy of children with CHD has improved, this population increasingly seeks medical attention for other illnesses, and a significant number of these patients will undergo non-cardiac surgeries.[25,26,27] To date, studies addressing mortality and adverse outcomes in children with and without CHD undergoing non-cardiac surgery have largely been performed at single centers and have included small patient numbers.[28,29,30] Recently, our group used a large dataset to demonstrate that children with major and severe CHD undergoing non-cardiac surgery have an increased risk of mortality, and a higher incidence of postoperative re-intubation compared to matched controls undergoing comparable procedures.[31]

Etomidate is NOT Benign

Etomidate, alone or in combination with other agents, is a popular agent for induction of anesthesia in children with compromised hemodynamics. A recent exceptionally well controlled clinical trial clearly demonstrates that a single induction dose of etomidate depresses cortisol levels for 24 hours in healthly children.[32] Enthusiasm for this drug should be tempered given these findings and the availability of other induction agent combinations such as ketamine in combination with fentanyl/remifentanil that minimally affect hemodynamics.

SpO_2 Decreases Laryngoscopy Can be Forestalled in Infants and Small Children

A very simple, intuitively obvious technique to insufflate oxygen into the posterior pharynx in conjunction with the AirTraq device has been demonstrated to forestall the

decrease in SpO_2 from 100% to 95% by 35 seconds in infants and small children.[33] The beauty of this concept is that with a little ingenuity it can be modified and used with any airway visualization device. The increased time afforded would be particularly useful during difficult intubation attempts and during intubation attempts by trainees. The value of this technique becomes more apparent when new information about the kinetics of SpO_2 decreases during apnea is taken into consideration. Oxygen Reserve Index (ORI) as determined by new pulse oximetry technology demonstrates the rapid decline in SpO_2 that occurs once oxygen reserve is exhausted with SpO_2 falling from 100% to 98% in 30 seconds and from 98% to 90% in 60 seconds.[34]

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