IARS

International Anesthesia Research Society

Review Course Lectures

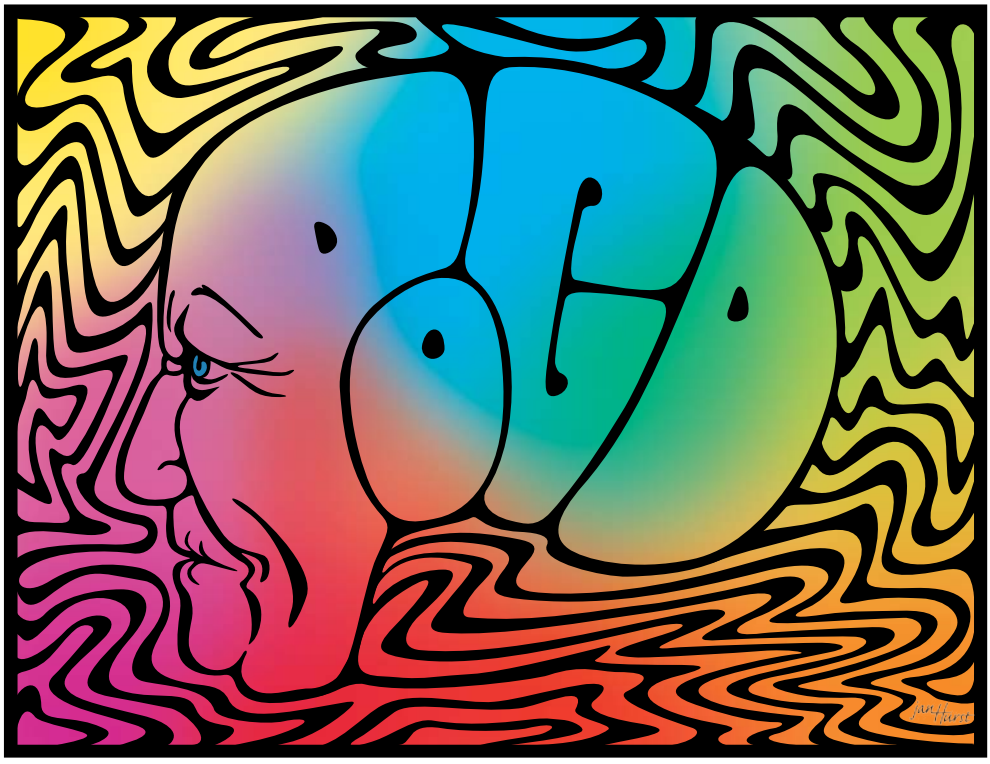
presented at the

2011 Annual Meeting of the

International Anesthesia Research Society

Vancouver, British Columbia, Canada

May 21-24, 2011



The material included in the publication has not undergone peer review or review by the Editorial Board of Anesthesia and Analgesia for this publication. Any of the material in this publication may have been transmitted by the author to IARS in various forms of electronic medium. IARS has used its best efforts to receive and format electronic submissions for this publication but has not reviewed each abstract for the purpose of textual error correction and is not liable in any way for any formatting, textual, or grammatical error or inaccuracy.

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

Table of Contents

©International Anesthesia Research Society. Unauthorized Use Prohibited.

Perioperative Implications of Emerging Concepts in Vascular Aging, Health, and Disease

Charles W. Hogue, MD
The Department of Anesthesiology & Critical Care Medicine
The Johns Hopkins University School of Medicine, Baltimore, MD

Despite a decline in mortality rates over the past four decades, cardiovascular disease remains the leading cause of morbidity and mortality in the US, affecting 80 million adults.[1,2] The prevalence and public health impact of cardiovascular disease is projected to steadily increase due to the general aging of the population and the rising incidence of obesity and hypertension.[2] The implications of an aging population with cardiovascular disease are important for the more than 20 million individuals who undergo surgery annually in the US, of whom, 10% will have a major complication within 30 days of surgery.[3,4] Adverse complications that affect the brain, such as delirium and postoperative cognitive dysfunction (POCD), are even more common. These conditions are distinct phenomena that disproportionately affect the elderly. Delirium is defined as an acute fluctuating disorder of consciousness, attention, cognition, and perception that cannot be explained by preexisting or evolving dementia (DSM-IV). Postoperative delirium occurs in 5% to 15% of patients but in as many as 16% to 62% of high-risk patients undergoing hip fracture surgery.[5,6] Postoperative delirium is independently associated with risk for prolonged hospitalization, medical complications, loss of independence, admission to a nursing home, reduced functional capacity, and mortality.[7-9] Delirium typically occurs ~24 hrs after surgery and resolves within 48 hrs, but it may persist until hospital discharge in 39% of patients and for 1 month after surgery in 33%.[10,11] POCD is a decrement from baseline in higher order thought processes involving learning, memory, attention, visual-spatial processing, abstract thinking, and executive function. The diagnosis of POCD requires psychometric testing, and thus, unlike delirium, deficits may not always be clinically manifested. Defining the frequency of POCD is problematic because the literature contains many methodological inconsistencies, including characteristics of the patients tested, psychometric battery used, timing of testing, definitions of decline, and other factors.6 Regardless, POCD has been suggested to occur in 12% to 30% of patients 3 months after cardiac surgery and in 10% to 13% of elderly patients after non-cardiac surgery.[12-14] The development of POCD is associated with longer hospitalization, altered quality of life, and early and late mortality.[6,14,15]

A further understanding of the effects of aging on the vasculature and its potential role in perioperative complications may foster strategies of care that lead to improved patient outcomes. In this lecture, a brief overview of vascular changes that occur with aging and their implications for the care of elderly patients undergoing surgery will be provided.

AGE-RELATED VASCULAR CHANGES

Chronological age is an established risk factor for vascular disease, yet age-associated changes in the vasculature vary greatly between individuals.16 Although there has been much focus on pathological abnormalities involving the intima (justifiably since this is the site of atherosclerosis and endothelial dysfunction), aging is associated with changes to all layers of the vasculature that lead to a generalized "stiffening" of central arteries. These changes can occur in the absence of atherosclerosis and form the basis of the growing concept of "vascular age" as a determinant of risk for adverse outcomes independent of chronological age.[16-18] In addition to providing prognostic information for ambulatory populations, it is now appreciated that arterial stiffness identifies risk for myocardial infarction, stroke, renal failure, and mortality after cardiac surgery.[19-22] Consequently, manifestations of vascular aging might provide the basis for more refined risk stratifications in balancing the risks and benefits of surgery.

Multiple mechanisms for age-related arterial stiffening have been identified, including increased deposition of collagen and increased fragmentation of elastin in the proximal aorta.[23,24] Media accumulation of matrix metalloproteinases and fibronectin may promote aortic wall thickening by promoting matrix protein degradation.[25,26] Furthermore, vascular smooth muscle cells have been found to increase in size in the media and migrate to the endothelium, an effect that might result from the binding of elastin-laminin fragments to specific smooth muscle and endothelial receptors.[27-29] Inflammatory processes also have been implicated in the pathophysiology of central artery wall and intimal thickening,[29] and the cross-linking of extracellular matrix proteins has been linked to arterial wall thickening.[30,31] A genetic predisposition to vascular stiffening has also been suggested, with polymorphisms of the angiotensin receptor, metalloproteinases, fibrillin-1, endothelin, and others implicated.[32-36]

MANIFESTATIONS OF CENTRAL VASCULAR STIFFNESS

The ejection of blood from the left ventricle generates a series of waves that are initially propagated antegrade, but then become retrograde when the waves are reflected at arterial bifurcations or by small arteries. The net arterial pulse wave, therefore, is a combination of both antegrade and reflected waves. In a healthy, compliant arterial system, reflected waves normally return to

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

the central circulation during diastole, enabling them to augment diastolic myocardial perfusion. In a stiff vasculature, the pulse waves reach the peripheral branch points faster, resulting in the reflected waves returning to the central circulation closer to systole.[37] Central arterial stiffness is manifest by increasing central aortic pressure or augmentation index, increasing pulse wave velocity, rising systolic pressure, declining diastolic pressure, and rising pulse pressure.[38,39] Recently, the larger contribution of forward waves generated by LV ejection than the reflected pulse waves to rising central aortic pressure and pulse pressure hypertension has been suggested.[40] Regardless, elevation of central aortic pressure increases left ventricular afterload, promoting left ventricular hypertrophy and diastolic dysfunction.[37] There are several clinical measures of vascular stiffness in addition to pulse pressure. Pulse wave velocity can be measured as the time interval between the EKG R wave and the peak of the pulse wave at two peripheral sites (usually the radial and femoral pulses) compared with more central pulses (usually the carotid pulse). This procedure can be performed with commercially available instruments that can also provide an estimate of central augmentation pressure derived mathematically from tonometrically obtained peripheral pulse waves.[18] Increased pulse wave velocity is an independent predictor of cardiovascular events and mortality in the general population.[18,41-43] The noninvasive nature of these measurements and their predictive capacity, which is are independent of age and other risk factors, supports their use in routine patient assessements.[44]

CEREBRAL CONSEQUENCES OF VASCULAR STIFFNESS

Normally, the central aorta has a cushioning function that dampens the energy of stroke volume and the reflected pulse waves.[37] A thickened, stiff central vasculature loses this protective mechanism, causing propagation of high pressure pulsatile waves to high-flow/low vascular resistance organs such as the brain and kidney. The result is chronic, compensatory arterial microcirculatory remodeling.[45-48] A vascular basis of cognitive impairment in the general population has been suggested based on multiple lines of evidence, including a link between these disorders and small-vessel disease that is manifest on brain images as small lacunar infarcts and white matter lesions.[37,49,50] Dementia is further linked to chronic vascular disease in risks and etiology.[49] Microvascular lesions (amyloid angiopathy, degeneration, basal lamina alterations, fibrosis) and luminal narrowing have been identified in brains of victims of Alzheimer's disease (AD).

An association between elevated pulse pressure and severity of cerebral white matter lesions indicative of brain microvascular narrowing has been reported.[46] Measures of aortic stiffness were independently found to predict stroke in patients with hypertension.[48] A more direct link between aortic stiffness and cognitive state was found in a study of 308 community-dwelling elderly (78±8 yrs) subjects with complaints of memory loss.[37] The individuals were categorized as having mild cognitive impairment (MCI, 27%), AD (41%), vascular dementia (VaD, 6%), or normal cognitive function (26%) based on standard examination and diagnostic criteria. A relationship was found between pulse wave velocity and cognitive state ($p<0.0001$) after adjustment for age, gender, systolic blood pressure, education level, cardiovascular disease, and antihypertensive drugs. Subjects with VaD (15.2±3.9 m/s), AD (13.3±2.9 m/s), and MCI (12.6±2.6 m/s) had higher pulse wave velocity than did those without cognitive impairment (11.5±2.0 m/s; $p<0.001$ vs VaD and AD; $p=0.01$ vs MCI). These investigators found that for each 2 m/s increase in pulse wave velocity, the adjusted odds ratio (95% CI) was 1.73 (1.27 to 2.47) for AD and 3.52 (1.87 to 8.05) for VaD.

Thus, the accumulating evidence strongly implies that age-associated aortic stiffness may contribute to the pathogenesis of cerebral microvascular changes associated with cognitive impairment. Additionally, there is a body of literature that suggests that the cumulative effect of cerebral lacunar infarcts, white matter lesions, and ischemic injury leads to progressing severity of cognitive deficits and ultimately dementia even though each individual lesion itself may not be severe enough to cause clinical deficits.[49] Endothelial dysfunction associated with vascular stiffness can further compromise cerebral blood flow and the blood-brain barrier.[37,45-48,51,52]

POSTOPERATIVE DELIRIUM AND POCD: A MANIFESTATION OF VASCULAR DISEASE?

The growing number of elderly patients with arterial stiffness and atherosclerosis is likely contributing to an increase in prevalence of cerebral vascular disease in surgical patients. Multiple series using brain MRI have revealed cerebral infarction in 40%–50% of patients before cardiac surgery.[3,53-59] These lesions are usually clinically asymptomatic, are associated with cerebral arterial stenosis, and increase the risk for new perioperative brain injury. Using SPECT imaging, Moraca et al.60 found that 75% of 82 patients had abnormal regional cerebral perfusion (defined as >2 SD below age-matched controls) before CABG surgery. Postoperative stroke occurred in 5% of patients and only in those with a preoperative regional perfusion defect. Our group has further reported on the high proportion of watershed strokes after cardiac surgery and the relationship between this hypoperfusion-associated injury and decreases in mean arterial pressure >10 mmHg from baseline on cardiopulmonary bypass.[61] Pre-existing cognitive dysfunction, a risk factor for POCD, is another manifestation of cerebral vascular disease in patients undergoing surgery. We found preoperative cognitive impairment in 49 of 108 (45%) elderly women scheduled for cardiac surgery using matched community-dwelling volunteers as controls.62 Advancing age, lower attained level of education, type 2 diabetes mellitus, and prior myocardial infarction were independent risk factors for cognitive impairment

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

($p<0.05$). Others have found cognitive impairment and neurological deficits in patients before surgery compared with normative data or non-hospitalized controls.[63,64] These studies underscore the importance of including a control group when assessing cognitive outcomes in surgical patients. In fact, Selnes et al.[65] found no differences in the rate of cognitive decline over a 6-year follow-up period between patients with coronary artery disease who received CABG surgery and similar patients who were treated by percutaneous coronary artery interventions. These data suggest that the natural history of cardiovascular disease, rather than anesthesia and surgery, accounts for longitudinal decrements in cognition over time.

The etiology of POCD after non-cardiac surgery is not known. In patients undergoing cardiac surgery, POCD is believed to result in brain injury of insufficient severity to result in stroke and/or it is restricted to brain areas involved with cognitive functions.14 Whether POCD is the direct result of brain injury after non-cardiac surgery is not clear.6 A relationship between postoperative delirium and serum biomarkers of central nervous system injury (S-100β and neuron-specific enolase) after cardiac and abdominal surgery has been reported.66,67 Risk models for delirium recognize the interaction between pre-existing patient vulnerability and acute precipitating factors. It has been proposed that the greater the number of pre-existing vulnerability factors, the fewer acute precipitating factors (e.g., visual impairment, severe illness, cognitive impairment, and dehydration) necessary for delirium to develop.68 Strategi es to reduce postoperative delirium have focused on correction of metabolic abnormalities (e.g., glycemic control, electrolytes), hydration, avoidance of hypoxemia, avoidance of drugs with central anticholinergic effects, avoidance of benzodiazepines, postoperative analgesia, ICU sedation, depth of sedation during regional anesthesia, and other general measures.5,9,68-77 Neurotoxic effects of anesthetics or their modulation of central neurotransmission have been the focus of speculation and intense investigation.6

Perioperatively, thickened arterioles might necessitate higher blood pressure for brain and other vital organ perfusion.[37,78] Hypotension is common during anesthesia and surgery and often viewed as a safe practice to reduce surgical bleeding.[20,69,79] The role of hypotension or hypoxemia in POCD, though, has not been clearly defined.[12] Williams-Russo[80] et al. randomized patients (mean age, 72 yrs) undergoing hip replacement surgery to intraoperative blood pressures of 45–55 mmHg or 55–70 mmHg. Cognitive outcomes did not differ between the two groups at 1 week or 4 months after surgery. The rate of delirium was low in this study, but its frequency was twice as high in patients in the low blood pressure group (9% vs 4%). Ramlawi et al.[81] investigated the role of intraoperative factors in the development of postoperative delirium and found no difference in the frequency of hypotension for patients with or without delirium. In that study, the definition of hypotension was based on review of the anesthesia record, where blood pressure was hand recorded every 5 min. Using a computerized anesthesia record to define blood pressure, Yocum et al.[82] found a relationship between minimum intraoperative mean arterial pressure and cognitive dysfunction 1 day and 1 month after spine surgery but only for patients with hypertension. Thus, the relationship between intraoperative blood pressure and delirium appears to depend on whether blood pressure is continuously and automatically recorded or intermittently hand recorded in the medical record.

Because "low" blood pressure has no widely accepted definition, some patients are placed at risk for cerebral ischemia when standard blood pressure management is used.[83] Basing blood pressure targets on more precise patient monitoring might be an approach for improving outcomes. Normally, blood flow to the brain is autoregulated over a range of blood pressures to maintain a steady supply of oxygenated blood. Keeping the blood pressure within the autoregulation range might be a more precise method for patient management than empiric blood pressure targets. Continuous, real-time cerebral blood flow (CBF) autoregulation can be monitored by measuring the moving correlation coefficient between blood pressure and transcranial Doppler-derived CBF velocity.84-86 Optimizing blood pressure within the CBF autoregulatory range has been shown to be associated with improved outcomes for patients with traumatic brain injury.87 In laboratory and human investigations, our group has shown that CBF autoregulation can be reliably monitored noninvasively with near-infrared spectroscopy.85,88,89 Individualizing blood pressure targets to be above a patient's lower autoregulatory threshold might prevent cerebral hypoperfusion during cardiac and non-cardiac surgery. Current trials in cardiac surgery (www.clinicaltrials.gov, NCT00769691) and orthopedic surgery performed in the "beach chair" position (www.clinicaltrials.gov, NCT01225185) may provide insights into this problem as well as help define new methods of patient monitoring.

REFERENCES

1. Circulation 2010;121:e46
2. JAMA 2010;304:2057-8.
3. DHHS publication 02-0428.
4. Ann Surg 1998;228:491-507.
5. Br J Anaesth 2009;103:i41-i6.
6. J Am Coll Cardiol 2000;36:685-92.
7. Lancet 2001;357:1264-5.
8. Mayo Clin Proc 2010;85:18-26.
9. J Am Geriatr Soc 2000;48:618-24.
10. Gerontology 2000;46:36-43.
11. Lancet 1998;351:857–61.
12. Anesthesiology 2008;108:18-30.
13. Anesth Analg 2006;103:21-37.
14. Anesthesiology 2008;108:18-30.
15. Hypertension 2005;46:454-62.
16. Circulation 2003;107:139-46.

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

17. Circulation 2006;113:657-3.
18. Circulation 2007;115:733-42.
19. Hypertension 2007;50:630-5.
20. Anesth Analg 2008;107:1122-9.
21. Anesth Analg 2010;110:335-40.
22. Hypertension 2005;45:652-8.
23. Circulation 1992;86:III68-III73.
24. Circulation 1994;90:1757-64.
25. JAMA 2004;291 1720-9.
26. Exper Molecular Pathology 1997;64:1-11.
27. Nature 1998;394:894-7.
28. Arterioscler Thromb Vasc Biol 2005;25:932-43.
29. Am J Physiol 2009;296:H1926-H32.
30. JAMA 2009;302:849-57.
31. Circulation 1996;94:698-703.
32. Circulation 2002;105:810-5.
33. Circ Res 2003;92:1254-61.
34. Am J Hypertens 2001;14:755-60.
35. Stroke 2005;36:2193-7.
36. Circulation 1997;96 308-15.
37. Hypertension. 2001;38 1461-6.
38. Circulation 2010;122:1379-86.
39. Circulation 2006;113:664-70.
40. Eur Heart J.
41. J Am Coll Cardiol;55:1318-27.
42. Clin J Am Soc Nephrol 2008;3:184-92.
43. Circulation 2003;108:2230-5.
44. Neuroepidemiology 1997;16:149-62.
45. Hypertension 2005;46:200-4.
46. Stroke;34:1203-6.
47. J Neurol 1997;244:135–42.
48. Neurology 1994;44:1246-52.
49. Neurobiol Aging 1986;7:489-502.
50. JAMA 1979;242:2193-6.
51. Circulation 2010;121:853-62.
52. J Neurosurg Anesthesiol 1994;6:163-9.
53. Arch Neurol 1998;55:618-27.
54. Ann Thorac Surg 1992;53:807-12.
55. Arch Neurol 2001;58:571-6.
56. Stroke 2002;33:2909-15.
57. Stroke 2004;35:888-92.
58. J Thorac Cardiovasc Surg 2006;131:540-6.
59. Stroke 2006;37:2306-11.
60. Anesth Analg 2006;102:1602-8.
61. Br J Anaesth 2001;86:63–7.
62. J Intern Neuropsychol Soc 1997;3:480–4.
63. Ann Neurol 2008;63:581-90.
64. Stroke 2000;31:645-50.
65. Br J Anaesth 2000;84:242-4.
66. JAMA 2001;286:2703-10.
67. Anesth Analg 1995;80:1223-32.
68. Br J Anaesth 1994;72:286-90.
69. Anesthesiology 2006;104:21-6.
70. Eur J Anaesthesiol 2010;27:411-6.
71. Anesth Analg 2006;102:1255-66.
72. Anesth Analg 2006;102:267-73.
73. JAMA 2009;301:489-99.
74. JAMA 2007;298:2644-53.
75. Circulation 2009;120:2271-306.
76. J Neurosci Res 1991;30:673-81.
77. Clin Orthop Rel Res 1974;101:93-8
78. Anesthesiology 1999;91:926-35.
79. J Thor Cardio Surg 2007;134:996-1005.
80. Anesthesiology 2009;110:254-61.
81. Anesthesiology 2007:213-20.
82. Neurocrit Care 2009;10:373-86.
83. Stroke 2007;38:2818-25.
84. Stroke 2010;41(9):1951-6.
85. Crit Care Med 2002;30:733-8.
86. NEJM 2009;360:2176-90.
87. Anesth Analg 2010;111:191-5.
88. J Geron A Biol Sci Med Sci 2003;58:M461–7.

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

Perioperative management of pain and PONV in ambulatory surgery

Spencer S. Liu, MD
Clinical Professor of Anesthesiology
Weill College of Medicine at Cornell University, Hospital for Special Surgery
New York, NY, USA

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

OPTIMIZATION OF ANALGESIA:

General anesthesia techniques

- Recent studies have reported the possibility of reduced postoperative pain after ambulatory procedures with the use of a propofol based anesthetic versus a volatile based anesthetic.[2] Although propofol does have analgesic properties, these findings are inconsistent. Furthermore, the magnitude of effect is limited. Opioid use is not markedly reduced, and postoperative pain scores are only marginally decreased for a relatively brief duration (< 12 hrs).

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

Regional anesthesia techniques

- A previous meta analysis has examined RCTs comparing GA with central neuraxial and peripheral nerve blocks for anesthesia.[5] Central neuraxial techniques were mixed for comparative outcomes with lower pain scores and less nausea but a longer time until discharge from the ASU (mean of 35 min). In contrast, use of peripheral nerve blocks was generally superior with less pain and nausea, faster discharge, and greater patient satisfaction.

- These beneficial effects of peripheral nerve blocks can now be extended to the home for patients with the advent of perineural catheters with portable or disposable pumps. A meta-analysis has examined RCTs that compared perineural catheters dosed with local anesthetic vs saline.[6] All groups had free access to systemic opioids. The perineural catheters with local anesthetics were clearly superior with lesser pain scores at rest and activity for 48 hrs after surgery. The active catheters had reduced opioid use with reduction in nausea, sedation, and pruritus.

- Several clinical studies have also reported other benefits with use of perineural techniques for ambulatory surgery. Use of femoral nerve analgesia after ACL reconstruction is associated with less pain and nausea in the PACU with increased ability to bypass Phase 1. Importantly, prolonged analgesia may have helped prevent unplanned hospital admission, as 78% of unplanned admissions did not have femoral nerve analgesia. Another RCT examined effects of perineural analgesia versus IV PCA at home after ambulatory surgery.[7] Perineural analgesia (interscalene or popliteal catheters) improved pain control, reduced opioid related side effects, and significantly increased patients' ability to perform activities of daily living at home.

- Recent pilot studies (n<15) have explored the feasibility and cost savings of converting typical hospitalized surgical procedures such as total hip, knee, and shoulder replacement into 23:59 hr hospital stays with the use of perineural analgesia (lumbar plexus, femoral nerve, and interscalene catheters).[8,9] These pilot programs have successfully discharged selected patients after an overnight stay without complications and with reduction in hospital cost. However, numerous concerns will need to be addressed prior to greater implementation. Concerns include shifting postoperative care to home and the ability to rescue patients from major complications at home. Previous surveys have noted a 2-6% incidence of major postoperative complications after total joint replacement such as pulmonary embolus or congestive heart failure.[10] Importantly, such complications are delayed in onset with peak occurrences on POD2-3.

Postoperative multimodal systemic analgesia

- NSAIDs: Meta analyses indicate that NSAIDs are highly useful analgesic adjuncts. They consistently reduce pain scores, reduce opioid

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

use and opioid related side effects. However, prolonged use of NSAIDs is associated with cardiovascular risk, renal impairment, and increased bleeding for some surgical procedures (tonsils). These findings were called into recent question due to retraction of a substantial number of RCTs by Dr. Reuben that investigated these agents. However, re-examination of meta-analyses demonstrated that prior findings remained robust.[11]

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

Alternative medicine techniques

- Multiple modalities have been examined including acupuncture, music, therapeutic suggestion, and static magnets. The best evidence exists for acupuncture.[13] Recent systematic reviews indicate that acupuncture can reduce pain scores, opioid consumption, and opioid related side effects such as PONV, pruritus, and sedation.

- The other modalities have not displayed efficacy for analgesia or reduction of PONV

PONV

- SAMBA has published consensus guidelines for management of PONV per figure below.[14]

- Recent developments include
  - o Palonosetron is a 5HT3-RA that is not a serotonin molecular structure mimic and does not bind at serotonin binding site. Thus, it may bind more tightly to serotonin receptors and may promote internalization of 5HT3 receptor. Palonosetron may have a longer duration of action and may be effective for up to 72 hrs.[15]

  - o Potential use of haloperidol as a D2 receptor antagonist, due to the FDA Black box warning for droperidol. Haloperidol has a faster onset and longer half life than droperidol, but has shorter duration of action due to less receptor binding. Studies suggest that doses of 0.5 -4 mg are effective vs placebo for 24 hrs with a NNT 3.2-5.1. Optimal dose, timing, and safety profile have yet to be determined

  - o Neurokinin-1 antagonists (Aprepitant) act both centrally and peripherally and may be superior to ondansetron for first 24 hrs

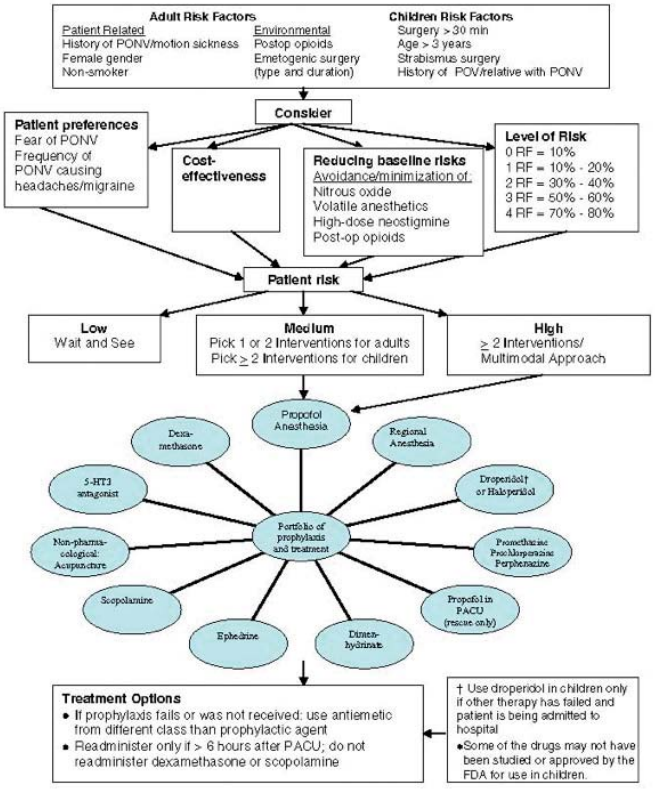


Figure 3. Algorithm for management of postoperative nausea and vomiting (PONV).

REFERENCES

1. Anesthesiology 2009:110:1061
2. Anesth Analg 2010:111:83
3. Br J Surg 2008:95:1331
4. Anesth Analg 2009:109:1805
5. Anesth Analg 2005:101:1634
6. Anesth Analg 2006:102:248
7. Anesthesiology 2006:105:566
8. RAPM 2006:31:113
9. RAPM 2007:32:46
10. JBJS 2008:89:27
11. Anesthesiology 2009:111:1279
12. Anesth Analg 2007:104:1545
13. Anesth Analg 2008:106:611
14. Anesth Analg 2007:105:1615
15. Int Anesthesiology Clin 2010:28:225

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

Colloid or Crystalloid: Any Differences in Outcomes?

Tong J. Gan, M.D., M.H.S., F.R.C.A.
Professor and Vice Chair, Department of Anesthesiology,
Duke University Medical Center, Durham, NC

INTRODUCTION

The choice of colloid or crystalloid as the optimal intraoperative resuscitation fluid remains unresolved, and disagreement exists over the selection of crystalloid or colloid as the optimal resuscitation fluid.[1,2] There are inherent differences between colloids and crystalloids that contribute to their effects. Colloids have a larger molecular weight, and hence expand the intravascular compartment more effectively.[3,4] Specifically, colloids have been shown to improve oxygen transport, myocardial contractility and cardiac output.[5,6]Arguments in favor of using crystalloids include the observations that they expand the extracellular compartment more effectively with less increase in extravascular pulmonary water as a result of rapid equilibration.[7,8] Crystalloids also minimize the risk of anaphylactoid reactions and cost less than colloids.[9,10] However, crystalloid reduces colloid oncotic pressure and may predispose to pulmonary edema 3 and bowel edema.[11] Tissue edema may also interfere with tissue oxygen exchange and delay in wound healing.[12]

TYPES OF FLUID

Intravenous fluids may broadly be classified into colloid and crystalloid solutions. They have very different physical, chemical and physiological characteristics (Tables 1 and 2).

CRYSTALLOID SOLUTIONS

Solutions of inorganic ions and small organic molecules dissolved in water are referred to as crystalloids. The main solute is either glucose or sodium chloride (saline) and the solutions may be isotonic, hypotonic or hypertonic with respect to plasma. Isotonic saline has a concentration of 0.9% w/v (containing 0.9g NaCl in each liter of water). Potassium, calcium, and lactate may be added to more closely replicate the ionic makeup of plasma (Table 1). Crystalloids with an ionic composition close to that of plasma may be referred to as "balanced" or "physiological".

Significant plasma volume expansion requires large volume crystalloid infusion. This causes a significant expansion of the extracellular volume that leads to tissue edema. Large volume crystalloid resuscitation following major burns is associated with significant tissue edema when compared with colloid resuscitation.[13] Theoretically this will result in increasing diffusion distances within tissues and compression of small vessels and capillaries result in compromised end-organ perfusion and oxygenation. Animal studies demonstrate that crystalloid infusion is associated with significant tissue fluid accumulation[14,15] but it is unclear as to whether this is greater than that which occurs following colloid administration.[16,17] Similarly data on whether tissue oxygen extraction is altered by accumulation of interstitial fluid is inconclusive with evidence in support of[14,18] and refuting this proposition.[19] Kimberger et al[20] in a pig hand-sewn colon anastomosis model recently showed that goal directed colloid resuscitation was associated with a greater degree of perioperative increase in tissue oxygen tension and microcirculatory blood flow compared with goal directed crystalloid administration.

Prien and colleagues 11 demonstrated that, in patients undergoing Whipple's procedure, crystalloid

Table 1. Comparison of contents, osmolarity and pH of crystalloid solutions for intravenous administration.

Solution	Osmolarity mOsmol/L	pH	Na^+mmol/L	Cl^-mmol/L	K^+mmol/L	Ca^{2+}mmol/L	Glucose mg/L	HCO_3^- mmol	Lactate mmol/L	Energy Kcal/L
Glucose 5%	252		-	-	-	-	50	-	-	400
Glucose 25%	1260		-	-	-	-	250	-	-	2000
Glucose 50%	2520		-	-	-	-	500	-	-	4000
Sodium Chloride 0.9%	308	5.0	154.0	154.0	-	-	-	-	-	-
Sodium Chloride and Glucose	264		31.0	31.0	-	-	40	-	-	320
Ringer's solution	309		147.0	156.0	4.0	2.2	-	-	-	-
Compound Sodium Lactate *	278		131.0	111.0	5.0	2.0	-	-	29.0	-
Plasmalyte B	298.5	5.5	140	98	5	-	-	50	-	-
Normasol+	280	7.4	140	98	5					

*Compound sodium lactate = Hartmanns' solution or Ringer's Lactate solution.
+Normasol contains acetate 27 mmol/L and gluconate 23 mmol/L

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

Table 2. Comparison of colloid solutions for intravenous administration.

Solution	Colloid Type	MWn/MWw KDaltons	DS	Na^+mmol/L	Cl^-mmol/L	K^+mmol/L	Ca^{2+}mmol/L	Glucose mg/L
Hespan 6%	Hetastarch	70/450	0.7	150	150	-	-	-
Hextend	Hetastarch	70/450	0.7	143	124	3	5	90
EloHaes 6%	Pentastarch	60/250	0.5	154	154	-	-	-
HAES-steril 6% or 10%	Pentastarch	70/250	0.5	154	154	-	-	-
Pentaspan 10%	Pentastarch	70/250	0.45	154	154			
Voluven	Tetrastarch	60/130	0.4	154	154			
Volulyte	Tetrastarch	60/130	0.4	137	110	4		
Gelofusine (4%)	Succinylated Gelatin	30	-	154	154	-	-	-
Haemaccel (3.5%)	Polygeline	30	-	145	145	5.1	6.25	-
Gentran 40	Dextran 40	40	-	154	154	-	-	-50
Gentran 70	Dextran 70	70	-	154	154	-	-	50
Rheomacrodex	Dextran 40	40	-	154	154	-	-	50
Macrodex	Dextran 70	70	-	154	154	-	-	50

Hextend also contain magnesium 0.9 mmol/L and lactate 28 mmol/L.
Volulyte also contain magnesium 1.5 mmol/L and acetate 34 mmol/L.

resuscitation with LR resulted in a significant increase in the water content of a jejunal specimen compared with intraoperative resuscitation with hetastarch or albumin. Intestinal edema has been associated with impaired gastrointestinal function intolerance for enteral nutrition,[21,22] an increase potential for the development of bacterial translocation, and the development of multiple organ dysfunction syndrome.[23,24]

Glucose solutions are available as isotonic (5% w/v containing 50g glucose in each liter of water) or hypertonic solutions (25% and 50% w/v). The small amount of glucose in the isotonic solution is rapidly metabolized allowing the solvent water to freely distribute throughout total body water. Isotonic glucose solution should be prescribed to treat simple dehydration and provide water replacement. The hypertonic glucose solutions are given to provide glucose as a metabolic substrate in hypoglycemia or in combination with insulin therapy.

Hypertonic solutions are commonly considered to be irritant to veins because of their high osmolarity and it is recommended that they be given into large veins or centrally although the evidence base for this advice is sparse. A limited study using 7.5% saline/6% dextran 70 failed to demonstrate any vessel damage following brief (2 min) rapid infusion through cephalic vein or femoral artery.[25] However 11.7% saline, which is the minimum effective concentration for use as clinically as a sclerosing agent,[26] has been demonstrated to cause immediate clinical and histological endothelial damage and thrombosis when infused into small veins in animal models.[27] Parenteral nutrition solutions up to 3 times normal osmolarity seems to be readily tolerated by peripheral veins[28] suggesting that the weaker hypertonic solutions (e.g. 1.8% Saline) can safely be administered peripherally.

COLLOID SOLUTIONS

A colloid is a homogeneous non-crystalline substance consisting of large molecules or ultramicroscopic particles of one substance dispersed through a second substance - the particles do not settle and cannot be separated out by ordinary filtering or centrifuging like those of a suspension such as blood. Colloid solutions used in clinical practice for fluid therapy are divided into the semisynthetic colloids (gelatins, dextrans and hydroxyethyl starches) and the naturally occurring human plasma derivatives (human albumin solutions, plasma protein fraction, fresh frozen plasma, and immunoglobulin solution). Most colloid solutions are presented with the colloid molecules dissolved in isotonic saline but isotonic glucose, hypertonic saline and isotonic balanced or "physiological" electrolyte solutions are also used. See Table 2.

Colloid molecular size can be highly variable. The semisynthetic colloids and the various preparations of plasma proteins in solution (e.g. fresh frozen plasma, plasma protein fraction) have a wide distribution of molecular sizes and are described as polydisperse. Human albumin solution contains more than 95% albumin with a uniform molecular size and is described as monodisperse. The size weight relationship is in most cases relatively constant although some colloids of equivalent molecular weight (MW) can have different molecular sizes (e.g. succinylated and urea linked gelatins have similar molecular weights but the succinylated product is physically larger due to increase in negative charge causing a conformational change). Colloid MW can be described as the weight averaged MW (MWw: the number of molecules at each weight multiplied by the particle weight divided by the total weight of all the molecules) or number averaged MW (MWn: the arithmetic mean of all particle MWs). The pattern of weight distribution can also be described by

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

the ratio of osmotic activity of a colloid solution across membranes with different pore sizes: the COP ratio.[29]

GELATINS

Gelatins are prepared by hydrolysis of bovine collagen. Succinylated gelatin (Gelofusin™) is produced by enzymatic alteration of the basic gelatin peptide and is presented in isotonic saline. Succinylation causes a conformational change that increases molecular size without significantly increasing molecular weight.[30] Urea linked gelatin (polygeline, Haemaccel™) is produced by thermal degradation of the raw material to small peptides (12000 to 15000 Dalton) followed by urea cross-linking to produce polymers of around 35000 Daltons[31] and is presented in an isotonic solution of sodium chloride with 5.1 mmol/L potassium and 6.25 mmol/L calcium.[32] Because of the significant calcium content of Haemaccel™ blood should not be infused through a giving set that has been previously used for this product.

Concerns have been raised about the risks associated with bovine derived gelatin because of the association between new variant Creutzfeld-Jakob disease (CJD) and Bovine Spongiform Encephalitis (BSE). All reported cases implicate bovine derived food products and there are no known cases of transmission involving pharmaceutical gelatin preparations. Most clinicians continue to use bovine gelatin based products; however, given the uncertainties concerning the transmission and behavior of BSE awareness of this issue is important.[33-35]

DEXTRANS

Dextrans are biosynthesized commercially from sucrose by Leuconostoc bacteria using the enzyme dextran sucrase.[36] The high molecular weight dextrans produced are then cleaved by acid hydrolysis and separated by repeated ethanol fractionation into a final product with a restricted molecular weight range. The products of this process are D-glucose polymers joined largely by alpha 1,6 bonds into predominantly linear macromolecules. They are defined by their MWn: Dextran 40 and Dextran 70 having MWns of 40,000 and 70,000 Daltons respectively.[30] Dextrans are polydisperse and clearance is dependant upon molecular weight. Dextran molecules of less than 50-55,000 Daltons are freely filtered at the renal glomerulus and around 70% of an administered dose of Dextran 40 will be excreted into the urine within 24 hours. Larger molecules are excreted through the gut or metabolized by endogenous dextranases in reticuloendothelial cells.[37]

ALBUMIN AND PLASMA PROTEIN FRACTION

The use of human derived colloid has a number of significant disadvantages including high cost and the theoretical risk of transmission of infectious agents such as New Variant Creutsfeld-Jakob disease associated with BSE. A systematic review of human albumin in the critically ill suggested that administration might increase mortality.[38] However this analysis was widely criticized for the heterogeneity of included studies. In most countries use of albumin in the management of hypovolemia is relatively uncommon because the semisynthetic colloids are believed to be at least as effective.

HYDROXYETHYL STARCHES

Hydroxyethyl starches (HES) are synthesized from amylopectin, a branching D-glucose polymer derived from maize or sorghum. Hydroxyethyl substitution by ethylene oxide occurs in the presence of an alkaline catalyst. The majority of substitutions occur at carbon 2 in the glucose ring, with a minority occurring at carbon 3 and 6, and a higher C2/C6 substitution ratio results in slower enzymatic degradation.[39] Hydroxyethylation slows hydrolysis by non-specific *-amylases in the blood; unsubstituted starch molecules are rapidly metabolized. The degree of substitution (DS), expressed as a number between 0 and 1, describes the proportion of substituted to non-substituted glucose moieties and an increased DS confers greater resistant to hydrolysis. The final product is produced by hydrolysis of the substituted starch to the required molecular weight followed by a purification process. Fractionation to produce narrower molecular weight bands is used for some products. The molecular weight profile and degree of substitution define the individual products. HES products can be divided into three classes by their MWw: high MW (450-480 KD), medium MW (around 200 KD) and low LW (70-130 KD). Examples of commercially available starches are 6% high MW hetastarch in saline (Hespan™), 6% high MW hetastarch in balanced electrolyes (Hextend™), medium MW pentastarch in saline (Elo-HAES™, HAES-steril™) and low MW tetrastarch in saline (Voluven) or in balance salt (Volulyte).

PROPERTIES OF COLLOIDS

The semisynthetic colloids are a heterogeneous group of products with each product having a defined set of properties. They vary in the magnitude and duration of plasma volume expansion, effects on hemorrheology and hemostatsis, interaction with endothelial and inflammatory cells, adverse drug reactions and cost.

The duration of plasma volume expansion produced by each colloid is governed by the rate of loss of colloid molecules from the circulation and by their metabolism. Rate of loss through the capillary endothelial barrier into the interstitial space and through the renal glomerulus into the urine is determined by molecular size (and therefore weight) and surface charge characteristics. The rate of intra- and extra- vascular metabolism is governed by specific chemical qualities of molecules (e.g. HES C2/C6 ratio and resistance to hydrolysis). The most useful descriptors of magnitude and duration of plasma volume expansion (PVE) are the intravascular half-life and the fraction of administered volume retained within the circulation after a specific time. Ninety minutes after administration of one liter

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

the gelatins produce a PVE of around 0.2L (equivalent to crystalloid) whereas Dextran and HES preparations produce a PVE of 0.7-0.8 liters.[40]

The predominant effect of colloid solutions on blood rheology (the physics of flow and deformation of matter) is to reduce whole blood viscosity by simple hemodilution thus improving blood flow characteristics.[41] The magnitude of this effect is proportional to the degree of plasma volume expansion and is therefore greater initially for the lower molecular weight (130,000 – 150,000 Dalton) HES and Dextran products that produce a large initial increment in intravascular volume and therefore a larger hemodilution effect. Independent of this dilutional increase in viscosity semisynthetic colloids also influence plasma viscosity and red cell aggregation that contribute to their overall effect on whole blood rheology. The higher molecular weight dextrans and hydroxyethyl starches cause an increase in plasma viscosity and the larger dextrans (e.g. Dextran 70) and gelatins also tend to cause red cell aggregation.[42] These effects are smaller in magnitude than the dilutional increase in whole blood viscosity but investigators are divided as to whether blood flow and tissue oxygenation can be compromised.[42,43] The lower molecular weight dextrans (eg. Dextran 40), starches and human albumin solution tend to cause reduced red blood cell aggregation and plasma viscocity[42,44] and this further enhances dilutional hypoviscosity resulting in increased flow particularly in the venous system.

All of the semisynthetic colloids have been shown to have an effect on hemostasis. This occurs partly as a result of simple hemodilution of clotting factors and partly due to colloid specific effects on components of the hemostatic mechanism. There is also increasing evidence that crystalloid hemodilution can induce a hypercoagulable state but the clinical significance is uncertain,[45,46] The gelatins appear to have the least impact on hemostasis however some abnormalities have been noted in over and above simple hemodilution of clotting factors. Gelatin use has been associated with reduced levels of Von Willebrand factor and factor VIIIc and studies with the thromboelastograph (TEG)[47] and sonoclot[48] technology suggest that clot strength may be reduced after large volume gelatin infusions. However there is little evidence that this results in increased blood loss or adverse bleeding events.[49] HES solutions have varying effects on hemostasis dependent on the molecular weight of the HES molecule.[50] Although conventional clotting indices are unaffected high molecular weight HES products in particular have been reported to produce a coagulopathy and this is thought to be associated with increased blood loss following surgery.[49,51,52] Impaired platelet function, a von Willebrand-like syndrome with reduced vWF and factor VIIIc, and impaired coagulation measured using the TEG have been reported and may explain these clinical findings.[53,54] Medium and low molecular weight HES preparations have been shown to produce similar, but lesser effects compared to the higher molecular weight products and it is believed that the risk of increased blood loss is minimal with these products.[50,55] The Dextrans are associated with more significant hemostatic derangements[56,57] and are effective antithrombotic agents.[58,59] In addition to simple hemodilution of clotting factors, low molecular weight Dextrans increase microvascular flow by platelet disaggregation and have specific effects on several components of the hemostatic system[60] Factor VIIIc and von Willebrands factor (vWF) are reduced, as is Factor VIII activity.[49] Red cell aggregation is also reduced with the lower molecular weight Dextrans. In patients whose hemostatic function is normal prior to infusion a maximum dose of 1.5-2g/kg is often recommended to avoid risk of bleeding complications.

Dextran and HES molecules may also have specific anti-inflammatory effects including reducing post-ischemic leukocyte-endothelial interactions and platelet adhesiveness.[37] In general the effect is stronger for Dextran preparations although Pentastarch (HES pentafraction) is thought to exert more pronounced inhibition of endothelial cell activation and neutrophil adhesion. Pentafraction is also believed to have specific benefits in retaining fluid within the capillaries, probably by physically plugging of endothelial pores, in situations where capillary leak occurs.[61]

Anaphylaxis or anaphylactoid events have been described in association with all of the semisynthetic colloids and albumin. The incidence of severe reactions (life-threatening event e.g. shock, life-threatening smooth muscle spasm, cardiac or respiratory arrest) is probably higher for Gelatins (highest reported incidence <0.35%) and Dextrans (<0.28%) than for albumin (<0.1%) or HES (<0.06%).[41] The advent of Dextran 1 hapten treatment has significantly reduced the risk of dextran related anaphylactic events to <0.0015%.[62] For comparison the rate of serious reactions to Penicillin is of the order of <0.05%. A significant incidence of itch has been noted with HES products by some authors.[63]

CRYSTALLOIDS VS. COLLOIDS

A longstanding controversy exists between crystalloid and colloid enthusiasts relating to the relative merits of the two fluid classes. The arguments center around the increase in edema associated with crystalloid therapy and the known adverse effects (hemostatic impairment, anaphylaxis etc) associated with colloid use. A large number of randomized controlled trials (RCTs) have been conducted to compare colloid and crystalloid fluid therapy in a variety of clinical settings although none have focused on mortality as an endpoint. Three systematic reviews have focused specifically on this issue.[64-66] Meta-analyses from the first two reviews suggested an increase in mortality associated with colloid use however the most recent analysis reported that " Methodologic limitations preclude any evidence-based clinical recommendations" and proposed large carefully designed RCTs to directly address this question. The majority of clinicians use a combination of crystalloid and colloid fluid therapy in the absence

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

of clear guidance from the available literature. Recent evidence suggests that colloid resuscitation may result in less edema and better quality of recovery in the postoperative period. Specifically, these patients had a lower incidence of nausea and vomiting and severe pain, which could be explained by the lower degree of tissue edema.[67]

PHYSIOLOGICALLY "BALANCED" VS. "UNBALANCED" FLUIDS

Large volume use of 0.9% saline, and of colloids dissolved in isotonic saline, is associated with the development of hyperchloremic metabolic acidosis due to the high chloride load.[51,68,69] Balanced or physiological fluids that contain inorganic ions (calcium, potassium or magnesium), molecular glucose, buffer components such as bicarbonate or lactate and have a lower chloride concentration are not associated with the same disturbance of acid/base physiology.[51,68,69] Recent data suggests that this acidosis may be clinically significant. Patients randomized to balanced solutions when compared with those randomized to saline based fluids had less impairment of hemostasis[46,70] and improved gastric perfusion.[51] Renal function may also be better preserved.[51] Balanced crystalloid solutions have been available for many years (e.g. Hartmann's solution – Ringer's Lactate). Colloid solution in a "balanced" 6% HES in a balanced electrolyte solution (Hextend®) are now widely available in the USA[70,71] and a low molecular weight balanced starch (Volulyte®) is also available in some parts of Europe and Asia.

In summary, the choice of fluid administration in the perioperative period can affect postoperative outcomes. Colloid results in a more effective plasma volume expansion compared to crystalloid and hence

lower volumes are required. Crystalloid is an essential part of perioperative fluid regimen for replenishing insensible and interstitial fluid loss. However, large volumes of crystalloid are associated with gastrointestinal dysfunction and delay bowel recovery. Balanced salt solutions appear to provide better postoperative outcomes than normal saline.

REFERENCES

1. 1. Grocott MP, Mythen MG, Gan TJ: Perioperative fluid management and clinical outcomes in adults. Anesthesia & Analgesia 2005; 100: 1093-106
2. 2. Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M: A rational approach to perioperative fluid management. Anesthesiology 2008; 109: 723-40
3. 3. Rackow EC, Falk JL, Fein IA, Siegel JS, Packman MI, Haupt MT, Kaufman BS, Putnam D: Fluid resuscitation in circulatory shock: a comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. Critical Care Medicine 1983; 11: 839-50
4. 4. Shoemaker WC, Schluter M, Hopkins JA, al e: Comparison of the relative effectiveness of colloids and crystalloids in emergency resuscitation. Am J Surg 1981; 142: 73-81
5. 5. Hauser CJ, Shoemaker WC, Turpin I, al e: Oxygen transport responses to colloids and crystalloids in critically ill surgical patients. Surg Gynecol Obstet 1980; 150: 811-16
6. 6. Hankeln K, Radel C, Beez M, al e: Comparison of hydroxyethyl starch and lactated ringer's solution on hemodynamics and oxygen transport of critically ill patients in prospective crossover studies. Crit Care Med 1989; 17: 133-35
7. 7. Tranbaugh RF, Elings VB, Christensen J, Lewis FR: Determinants of pulmonary interstitial fluid accumulation after trauma. Journal of Trauma-Injury Infection & Critical Care 1982; 22: 820-6
8. 8. Gallagher JD, Moore RA, Kerns D, Jose AB, Botros SB, Flicker S, Naidech H, Clark DL: Effects of colloid or crystalloid administration on pulmonary extravascular water in the postoperative period after coronary artery bypass grafting. Anesthesia & Analgesia 1985; 64: 753-8
9. 9. Moss GS, Lowe RJ, Jilek J, Levine HD: Colloid or crystalloid in the resuscitation of hemorrhagic shock: a controlled clinical trial. Surgery 1981; 89: 434-8
10. 10. Lowe RJ, Moss GS, Jilek J, Levine HD: Crystalloid vs colloid in the etiology of pulmonary failure after trauma: a randomized trial in man. Surgery 1977; 81: 676-83
11. 11. Prien T, Backhaus N, Pelster F, Pircher W, Bunte H, Lawin P: Effect of intraoperative fluid administration and colloid osmotic pressure on the formation of intestinal edema during gastrointestinal surgery. Journal of Clinical Anesthesia 1990; 2: 317-23
12. 12. Twigley AJ, Hillman KM: The end of the crystalloid era? A new approach to peri-operative fluid administration. Anaesthesia 1985; 40: 860-71
13. 13. Ahlborg G, Lundberg JM: Splanchnic release of neuropeptide Y during prolonged exercise with and without beta-adrenoceptor blockade in healthy man. Clinical Physiology 1991; 11: 343-51
14. 14. Baum TD, Wang H, Rothschild HR, Gang DL, Fink MP: Mesenteric oxygen metabolism, ileal mucosal hydrogen ion concentration, and tissue edema after crystalloid or colloid resuscitation in porcine endotoxic shock: comparison of Ringer's lactate and 6% hetastarch. Circ Shock 1990; 30: 385-97.
15. 15. Moon PF, Hollyfield-Gilbert MA, Myers TL, Kramer GC: Effects of isotonic crystalloid resuscitation on fluid compartments in hemorrhaged rats. Shock 1994; 2: 355-61.
16. 16. Bressack MA, Morton NS, Hortop J: Group B streptococcal sepsis in the piglet: effects of fluid therapy on venous return, organ edema, and organ blood flow. Circ Res 1987; 61: 659-69.
17. 17. Rackow EC, Astiz ME, Schumer W, Weil MH: Lung and muscle water after crystalloid and colloid infusion in septic rats: effect on oxygen delivery and metabolism. J Lab Clin Med 1989; 113: 184-9.
18. 18. Ostgaard G, Reed RK: Interstitial fluid accumulation does not influence oxygen uptake in the rabbit small intestine. Acta Anaesthesiol Scand 1995; 39: 167-73.
19. 19. Gotohda N, Iwagaki H, Itano S, Horiki S, Fujiwara T, Saito S, Hizuta A, Isozaki H, Takakura N, Terada N, Tanaka N: Can POSSUM, a scoring system for perioperative surgical risk, predict postoperative clinical course? Acta Medica Okayama 1998; 52: 325-9
20. 20. Kimberger O, Arnberger M, Brandt S, Plock J, Sigurdsson GH, Kurz A, Hiltebrand L: Goal-directed colloid administration improves the microcirculation of healthy and perianastomotic colon. Anesthesiology 2009; 110: 496-504
21. 21. Moss GS: Plasma albumin and postoperative ileus. Surg Forum 1967; 18: 333-6
22. 22. Falk JL: Fluid resuscitation and colloid-crystalloid controversy: New thoughts on an old debate. Crit Care Med 1991; 19: 451-53
23. 23. Baker JW, Deitch ED, Ma LM, al e: Hemorrhagic shock induces baterial translocation from the gut. J Trauma 1988; 28: 896-06
24. 24. Wilmore DW, Smith RJ, O'Dwyer ST, al e: The gut - a central organ following surgical stress. Surgery 1988; 104: 917-23
25. 25. Hands R, Holcroft JW, Perron PR, Kramer GC: Comparison of peripheral and central infusions of 7.5% NaCl/6% dextran 70. Surgery 1988; 103: 684-9.
26. 26. Sadick NS: Sclerotherapy of varicose and telangiectatic leg veins. Minimal sclerosant concentration of hypertonic saline and its relationship to vessel diameter. J Dermatol Surg Oncol 1991; 17: 65-70.
27. 27. Goldman MP: A comparison of sclerosing agents. Clinical and histologic effects of intravascular sodium morrhuate, ethanolamine oleate, hypertonic saline (11.7%), and sclerodex in the dorsal rabbit ear vein. J Dermatol Surg Oncol 1991; 17: 354-62.
28. 28. Bodoky A, Zbinden A, Muller J, Leutenegger A: [Peripheral venous tolerance of hyperosmolar infusion solutions]. Helv Chir Acta 1980; 47: 151-6.
29. 29. Mythen MG, Salmon JB, Webb AR: The rational administration of colloids. Blood Reviews 1993; 7: 223-8
30. 30. Salmon JB, Mythen MG: Pharmacology and physiology of colloids. Blood Reviews 1993; 7: 114-20
31. 31. Mishler JMt: Synthetic plasma volume expanders--their pharmacology, safety and clinical efficacy. Clin Haematol 1984; 13: 75-92.
32. 32. Saddler JM, Horsey PJ: The new generation gelatins. A review of their history, manufacture and properties. Anaesthesia 1987; 42: 998-1004

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

33. 33. Atherton P, Davies MW: Gelatin solutions. Anaesthesia 1996; 51: 989.

34. 34. Bedforth NM, Hardman JG: Mad colloid disease? Anaesthesia 1997; 52: 389-90.

35. 35. Marwick C: BSE sets agenda for imported gelatin. Jama 1997; 277: 1659-60.

36. 36. Mishler JM: Pharmacological effects produced by the acute and chronic administration of hydroxyethyl starch. J Clin Apheresis 1984; 2: 52-62.

37. 37. Haljamae H DM, Walentin F.: Artificial colloids in clinical practise: pros and cons. Bailliere's Clinical Anaesthesiology 1997; 11: 49-79

38. 38. Anonymous: Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. Lancet 2000; 355: 1295-302

39. 39. Treib J, Haass A, Pindur G, Seyfert UT, Treib W, Grauer MT, Jung F, Wenzel E, Schimrigk K: HES 200/0.5 is not HES 200/0.5. Influence of the C2/C6 hydroxyethylation ratio of hydroxyethyl starch (HES) on hemorheology, coagulation and elimination kinetics. Thrombosis & Haemostasis 1995; 74: 1452-6

40. 40. Lamke LO, Liljedahl SO: Plasma volume changes after infusion of various plasma expanders. Resuscitation 1976; 5: 93-102

41. 41. Audibert G, Donner M, Lefevre JC, Stoltz JF, Laxenaire MC: Rheologic effects of plasma substitutes used for preoperative hemodilution. Anesthesia & Analgesia 1994; 78: 740-5

42. 42. Freyburger G, Dubreuil M, Boisseau MR, Janvier G: Rheological properties of commonly used plasma substitutes during preoperative normovolaemic acute haemodilution. British Journal of Anaesthesia 1996; 76: 519-25

43. 43. Krieter H, Bruckner UB, Kefalianakis F, Messmer K: Does colloid-induced plasma hyperviscosity in haemodilution jeopardize perfusion and oxygenation of vital organs? Acta Anaesthesiol Scand 1995; 39: 236-44.

44. 44. Treib J, Haass A, Pindur G: Hetastarch Coagulopathy. Journal of Neurosurgery 1996; 85: 367-8; discussion 368

45. 45. Ruttmann TG, James MF, Viljoen JF: Haemodilution induces a hypercoagulable state. British Journal of Anaesthesia 1996; 76: 412-4

46. 46. Martin G, Bennett-Guerrero E, Wakeling H, Mythen MG, el-Moalem H, Robertson K, Kucmeroski D, Gan TJ: A prospective, randomized comparison of thromboelastographic coagulation profile in patients receiving lactated Ringer's solution, 6% hetastarch in a balanced-saline vehicle, or 6% hetastarch in saline during major surgery. Journal of Cardiothoracic & Vascular Anesthesia 2002; 16: 441-6

47. 47. Mardel SN, Saunders FM, Allen H, Menezes G, Edwards CM, Ollerenshaw L, Baddeley D, Kennedy A, Ibbotson RM: Reduced quality of clot formation with gelatin-based plasma substitutes. Br J Anaesth 1998; 80: 204-7.

48. 48. Brazil EV, Coats TJ: Sonoclot coagulation analysis of in-vitro haemodilution with resuscitation solutions. J R Soc Med 2000; 93: 507-10.

49. 49. de Jonge E, Levi M: Effects of different plasma substitutes on blood coagulation: a comparative review. Crit Care Med 2001; 29: 1261-7.

50. 50. Strauss RG, Pennell BJ, Stump DC: A randomized, blinded trial comparing the hemostatic effects of pentastarch versus hetastarch. Transfusion 2002; 42: 27-36.

51. 51. Wilkes NJ, Woolf R, Mutch M, Mallett SV, Peachey T, Stephens R, Mythen MG: The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. Anesthesia & Analgesia 2001; 93: 811-6

52. 52. Knutson JE, Deering JA, Hall FW, Nuttall GA, Schroeder DR, White RD, Mullany CJ: Does intraoperative hetastarch administration increase blood loss and transfusion requirements after cardiac surgery? Anesthesia & Analgesia 2000; 90: 801-7

53. 53. Tobias MD, Wambold D, Pilla MA, Greer F: Differential effects of serial hemodilution with hydroxyethyl starch, albumin, and 0.9% saline on whole blood coagulation. J Clin Anesth 1998; 10: 366-71.

54. 54. Claes Y, Van Hemelrijck J, Van Gerven M, Arnout J, Vermylen J, Weidler B, Van Aken H: Influence of hydroxyethyl starch on coagulation in patients during the perioperative period. Anesth Analg 1992; 75: 24-30.

55. 55. Langeron O, Doelberg M, Ang ET, Bonnet F, Capdevila X, Coriat P: Voluven, a lower substituted novel hydroxyethyl starch (HES 130/0.4), causes fewer effects on coagulation in major orthopedic surgery than HES 200/0.5. Anesthesia & Analgesia 2001; 92: 855-62

56. 56. Petroianu GA, Liu J, Maleck WH, Mattinger C, Bergler WF: The effect of In vitro hemodilution with gelatin, dextran, hydroxyethyl starch, or Ringer's solution on Thrombelastograph. Anesth Analg 2000; 90: 795-800.

57. 57. Mortier E, Ongenae M, De Baerdemaeker L, Herregods L, Den Blauwen N, Van Aken J, Rolly G: In vitro evaluation of the effect of profound haemodilution with hydroxyethyl starch 6%, modified fluid gelatin 4% and dextran 40 10% on coagulation profile measured by thromboelastography. Anaesthesia 1997; 52: 1061-4

58. 58. Kline A, Hughes LE, Campbell H, Williams A, Zlosnick J, Leach KG: Dextran 70 in prophylaxis of thromboembolic disease after surgery: a clinically oriented randomized double-blind trial. Br Med J 1975; 2: 109-12.

59. 59. Clagett GP, Reisch JS: Prevention of venous thromboembolism in general surgical patients. Results of meta-analysis. Ann Surg 1988; 208: 227-40.

60. 60. Bergman A, Andreen M, Blomback M: Plasma substitution with 3% dextran-60 in orthopaedic surgery: influence on plasma colloid osmotic pressure, coagulation parameters, immunoglobulins and other plasma constituents. Acta Anaesthesiologica Scandinavica 1990; 34: 21-9

61. 61. Webb AR, Moss RF, Tighe D, Mythen MG, al-Saady N, Joseph AE, Bennett ED: A narrow range, medium molecular weight pentastarch reduces structural organ damage in a hyperdynamic porcine model of sepsis. Intensive Care Medicine 1992; 18: 348-55

62. 62. Ljungstrom KG: Safety of dextran in relation to other colloids--ten years experience with hapten inhibition. Infusionsther Transfusionsmed 1993; 20: 206-10.

63. 63. Wheeler DW, van Heerden N: Itching after use of starch solutions [letter]. British Journal of Anaesthesia 1999; 83: 973-4

64. 64. Velanovich V: Crystalloid versus colloid fluid resuscitation: a meta-analysis of mortality. Surgery 1989; 105: 65-71

65. 65. Schierhout G, Roberts I: Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: a systematic review of randomised trials. Bmj 1998; 316: 961-4.

66. 66. Choi PT, Yip G, Quinonez LG, Cook DJ: Crystalloids vs. colloids in fluid resuscitation: a systematic review. Critical Care Medicine 1999; 27: 200-10

67. 67. Moretti E, Robertson KM, El-Moalem H, Gan TJ: Intraoperative colloid administration reduces postoperative nausea and vomiting and improves postoperative outcomes compared to crystalloid administration. Anesth Analg 2003; 96: 611-7

68. 68. McFarlane C, Lee A: A comparison of Plasmalyte 148 and 0.9% saline for intra-operative fluid replacement. Anaesthesia 1994; 49: 779-81

69. 69. Scheingraber S, Rehm M, Sehmisch C, Finsterer U: Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. Anesthesiology 1999; 90: 1265-70.

70. 70. Gan TJ, Bennett-Guerrero E, Phillips-Bute B, Wakeling H, Moskowitz DM, Olufolabi Y, Konstadt SN, Bradford C, Glass PS, Machin SJ, Mythen MG: Hextend, a physiologically balanced plasma expander for large volume use in major surgery: a randomized phase III clinical trial. Hextend Study Group. Anesthesia & Analgesia 1999; 88: 992-8

71. 71. Wilkes NJ, Woolf RL, Powanda MC, Gan TJ, Machin SJ, Webb A, Mutch M, Bennett-Guerrero E, Mythen M: Hydroxyethyl starch in balanced electrolyte solution (Hextend)--pharmacokinetic and pharmacodynamic profiles in healthy volunteers. Anesth Analg 2002; 94: 538-44.

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

Critical Care Update for 2011

Robert N. Sladen, MBChB, MRCP(C), FRCP(C), FCCM
Professor and Executive Vice-Chair, and Chief, Division of Critical Care
Department of Anesthesiology
College of Physicians & Surgeons of Columbia University, New York, NY

LEARNER OBJECTIVES:

- Update on mechanical circulatory support with the ventricular assist device: LVAD, RVAD and BiVAD.
- Update on management of elevated pulmonary vascular resistance, including inhaled nitric oxide, prostacyclin and other pharmacotherapy
- Update on management of vasodilatory shock, including vasopressin, selective vasopressin analogs and methylene blue
- Update on renal protection, including new biomarkers and the evidence basis for pharmacologic interventions.

THE VENTRICULAR ASSIST DEVICE (VAD)

Indications

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

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

ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

Correction of Structural Abnormalities

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

Pulmonary Vascular Resistance

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

Management of RV Function

Maintenance of effective RV function is essential to ensuring good outcome after LVAD placement.[1] Acute right heart failure (RHF) may occur in up to 40% of patients receiving an LVAD.[2] It is associated with an increased rate of reoperation for bleeding, postoperative acute kidney injury (AKI), ICU length of stay (LOS) and early mortality. Successful bridge to transplantation is impaired and about a third of the patients with RHF ultimately require an RVAD.

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

A fifth principle specific to newer LVADs is the avoidance of excessive LV emptying. Second and third generation LVADs provide non-pulsatile flow and maintain a parallel circuit of flow out of the native aorta. Excessive pump rates may cause the LV to empty, which induces leftward septal shift and RV dyskinesis. This may be revealed on transesophageal echocardiography (TEE) by conversion of the short-axis round LV to a "D"-shape induced by the flattened or convex intraventricular septum.[1]

Inodilator Therapy

Inodilator therapy is usually provided by the phosphodiesterase (PDE) III inhibitor, milrinone, with or without superadded dobutamine, a direct acting beta-1 and beta-2 agonist. These agents both increase cyclic adenosine monophosphate (cAMP),

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

the former by decreasing its breakdown and the latter by increasing its production. Milrinone's vasodilator effects may be limiting and invariably require concomitant vasopressors administration; dobutamine preserves blood pressure but its chronotropic and bathmotropic effects promote arrhythmias. Combining a PDE inhibitor with a beta-adrenergic agonist provides superior enhancement of RV stroke volume than either drug used alone,[3] and allows much lower dosage of each drug, with fewer side effects.

Levosimendan, a potent inodilator not currently available in the USA, acts independently of the beta receptor or cAMP by stabilization of the troponin C-calcium complex in myofibrils, strengthening the actin-myosin cross bond.[4] Levosimendan may have a more sustained benefit on postoperative stroke volume than milrinone and require less norepinephrine (NE) vasoconstrictor support.[5] In patients with low EF, the combination of levosimendan with dobutamine is more effective in improving stroke volume than the combination of milrinone and dobutamine. Levosimendan undergoes biotransformation to an active metabolite that exerts potent effects for up to a week, so it is not infused for more than 24 hrs, and there may be a benefit to starting the infusion 48 hrs before surgery.

FIRST GENERATION VADS: PULSATILE FLOW

Thoratec HeartMate XVE

The Thoratec HeartMate I or XVE became established as the LVAD that achieved the widest use in the decade from its introduction in 1994 through about 2005. It served primarily as a bridge to transplant, but in 2001 was shown to be superior to maximal medical therapy in survival as well as quality of life in destination therapy.[6] It has a large metallic pump placed sub-diaphragmatically but pre-peritoneally in the abdomen (LVAD pocket), with an inflow from the left ventricle (LV) and an outflow into the ascending aorta above the aortic valve. Porcine valves are placed in the inflow and outflow tubes just proximal and distal to the pump. The pump has a driveline that provides electrical power and emerges from the abdominal wall some distance from the LVAD pocket. The interior of the pump consists of a rotating flange that moves up (systole) and down (diastole) a circular cam, generating pulsatile flow out the aorta and essentially emptying the LV during each cycle.

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

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

The PVAD and IVAD

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

SECOND GENERATION VADS: NON-PULSATILE AXIAL (ROTARY) FLOW

Thoratec HeartMate® II

The Thoratec HeartMate® II is a pencil-like pump that rotates at 8000-10000 rpm and creates axial flow within a long term internal LVAD that has a number of advantages over its predecessor. It has virtually replaced the HeartMate® XVE as a bridge to transplant or destination therapy. The profile of the HeartMate® II is less than a quarter than that of the HeartMate® XVE, creating a much smaller LVAD pocket with no gastric compression, and allowing placement in small adults. It is much quieter, has far fewer moving parts, and much greater longevity. Compared to the HeartMate® XVE, the HeartMate® II provides significantly greater two year survival (58% vs. 24%) and freedom from disabling stroke or device malfunction (46% vs. 11%)7.

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

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

Because drainage from the LV is continuous, excessive flow generated by high rpm in the LVAD may cause the LV chamber to collapse, especially if the inflow cannula is sucked against the LV wall (a "suction event").[1] This in turn displaces the intraventricular septum and may acutely compromise RV function. A similar situation may be caused by intravascular hypovolemia. The relative volume (or unloading) status of the LV is indicated on the LVAD monitor by a unit-less parameter called the pulsatility index (PI), which must be closely assessed and kept between 4.0 and 6.0.

Pump flow is calculated based on power and blood viscosity; at the extremes of flow it is subject to error and may indicate "normal" flow in low flow states such as cardiac tamponade.[1] The nature of the device precludes polyurethane coating, so patients must be fully anticoagulated, which increases the risk of postoperative bleeding. However, thromboembolic cerebrovascular events appear to be if anything less common than with the HeartMate XVE (see above).

Abiomed® Impella® 5.0

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

THIRD GENERATION VADS: NON-PULSATILE CENTRIFUGAL FLOW

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

Terumo® DuraHeart™

The Terumo® DuraHeart™ is a third-generation long-term LVAD in which the pump is provided by a magnetically levitated impeller with centrifugal flow. In other respects its concept is similar to the HeartMate® II, with a small intra-abdominal, preperitoneal LVAD pocket, driveline and external battery packs. The device is approved in the European Union (EU), where compared to pulsatile LVADs it demonstrates significantly improved survival (85% at 6 months, 79% at 1 year), and only a 4% replacement rate at 2 years 8.

HeartWare® HVADTM

The HeartWare® HVADTM is a miniaturized third-generation LVAD in which the inflow cannula is cored directly into the LV apex so that the entire system is intrapericardial and above the diaphragm. It has a small driveline that is exteriorized and attached to small portable battery packs. The HVADTM is already approved in the EU and is undergoing extended trials in the USA as both bridge to transplant and destination therapy.

Levitronix® CentriMag

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

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

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

MANAGEMENT OF ELEVATED PULMONARY VASCULAR RESISTANCE (PVR)

Principles of Management

The pulmonary vascular resistance (PVR) is a critical determinant of RV afterload. The LV is made up of concentric muscle fibers geared toward the pressure work conferred by the systemic vascular resistance (SVR). In contrast, pressures in the RV are normally one-fifth those in the LV, and the RV fibers are arranged like those of a bellows, conducive to volume work. Acute elevation in PVR can cause the RV to rapidly decompensate, and must be treated promptly.[9,10]

The first step in treating elevated PVR is to treat abnormal physiologic states that exacerbate it, notably acidosis, hypercarbia, hypoxemia and excessive catecholamine activity (induced by pain, anxiety, hypovolemia, increased work of breathing etc.). If this is not done effectively, none of the pharmacologic interventions mentioned below will be effective either.

In the LV 70-90% of coronary perfusion occurs during diastole. Because the aortic diastolic pressure (ADP) is normally greater than the RV systolic pressure, RV coronary perfusion occurs throughout the cardiac cycle. When the PVR is markedly elevated, RV coronary

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

perfusion depends on the gradient between the ADP and the RV end-diastolic pressure (RVEDP). This is an important limitation of pulmonary vasodilators that also cause systemic vasodilation and hypotension. Systemic blood pressure can be maintained with vasopressors such as phenylephrine and NE,[11] but these agents may exacerbate pulmonary vasoconstriction at high doses. The co-administration of low doses (< 4 u/hr) of arginine vasopressin (AVP) does not induce pulmonary vasoconstriction and markedly decreases NE dose requirements, which may in turn benefit PVR.

INHALED NITRIC OXIDE (INO)

Mechanism of Action

Inhaled nitric oxide (INO) mediates pulmonary vasodilation through activation of soluble guanylate cyclase (sGC), which catalyzes the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP), a potent vascular smooth muscle relaxant.

Once inhaled, the nitric oxide molecule is rapidly inactivated in the pulmonary circulation by binding to heme proteins (including oxyhemoglobin, oxymyoglobin, guanylate cyclase, cyclooxygenase, and cytochrome P_{450}).

Therapeutic Benefits

Heme binding ensures that INO provides selective pulmonary vasodilation without any effect on the systemic circulation. The effect is dose dependent in the range of 5-40 ppm, and is proportionately greater with increasing degrees of pulmonary vasoconstriction.[10] Elevated PVR and mean pulmonary artery pressure (MPAP) are consistently decreased, while systemic blood pressure, ADP and RV coronary perfusion remain unaffected. The decrease in RV afterload in turn may enhance RV performance, with improvement in ejection fraction (EF) and RV end-diastolic volume (RVEDV).[12]

When administered after cardiopulmonary bypass (CPB), INO decreases elevated PVR and promotes RV recovery from transient ischemic injury, while maintaining LV filling by increasing pulmonary arterial blood flow. This is particularly helpful after placement of an LVAD, whose filling and ejection is very dependent on pulmonary venous return to the left atrium and LV.

Adverse Effects

By increasing pulmonary blood flow, INO increases LV filling. In patients with isolated LV dysfunction and poor ventricular compliance, this can result in a rapid increase in LV filling pressure, acute volume overload, ventricular failure and pulmonary edema.[13]

Acute, potentially life-threatening increases in PVR and MPAP can occur when INO is abruptly discontinued.[14] This may be the consequence of suppression of endogenous nitric oxide formation by down-regulation or inactivation of endogenous endothelial nitric oxide synthase (eNOS). INO improves ventilation-perfusion (VA/Q) matching by vasodilating the pulmonary circulation in the best-ventilated lung zones. Rapid weaning of INO < 5 ppm is often associated with worsening VA/Q and hypoxemia. Weaning of INO should always be done with close attention to its effects on oxygenation (SpO_2, PaO_2), PVR (MPAP) and RV function (CVP).

Delivery and Toxicity

INO dosage > 80 ppm provides an increasing risk of toxicity from the pro-inflammatory effects of nitric oxide itself or its reactive products. In the presence of high oxygen levels (i.e. at high FiO_2) nitric oxide forms toxic nitrogen dioxide (NO_2), which reacts with water to form nitric acid (HNO_3). It may also reacts with oxygen to form peroxynitrite (ONOO-), which rapidly decomposes to form NO_2 and the very reactive hydroxyl radical (OH-).

When nitric oxide binds to hemoglobin it oxidizes ferrous (Fe^{2+}) to ferric (Fe^{3+}) ion, to create methemoglobin (MetHb), which is incapable of binding oxygen. The degree of methemoglobinemia is INO dose-related, more likely in premature neonates or at doses > 40 ppm, and results in cyanosis, dyspnea and abnormal pulse oximetry readings.

Delivery Systems

At the present time there is only one distributor of INO and INO delivery systems (INOMAX®, Ikaria®), and as a consequence, INO is extremely expensive. However, it is essential to use such an approved delivery system for safe administration of INO. The injection module is inserted between the ventilator output and the humidifier, and INO is injected proportionally to the measured ventilator flow to provide the desired dose. Gas is sampled downstream in the inspPiratory circuit and analyzed electrochemically, and the display provides FIO_2, INO and NO_2 concentrations, with multiple alarms. The system can also be adapted to a manual bag system for transport, providing NO at 20 ppm.

SILDENAFIL

As specified above, the vasodilator effects of nitric oxide are mediated through activation of cGMP. Phosphodiesterase V (PDE V) converts cGMP to guanosine monophosphate (GMP) and thereby limits its duration of action. Administration of a selective PDE V inhibitor, sildenafil, enhances the duration of action of cGMP. In its own right sildenafil induces dose-dependent decreases in elevated PVR, but it also enhances the effect of INO, and attenuates acute pulmonary hypertension caused by abrupt INO withdrawal.

Sildenafil is approved as maintenance therapy in pulmonary arterial hypertension (PAH); it is dosed orally as 10-30 mg three times a day. In 2009 an intravenous (IV) preparation of sildenafil was approved which facilitates its use in the perioperative period; an IV dose of 10 mg is pharmacodynamically equivalent to an oral dose of 20 mg.[15] Sildenafil is not available as

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

an inhaled preparation, and its pulmonary effects are limited by unwanted systemic vasodilation.

INHALED PROSTACYCLINS

Mechanism of Action

Prostacyclin (PGI_2) is a vasodilator prostaglandin that induces smooth muscle relaxation by activating cyclic adenosine monophosphate (cAMP). There is both experimental and clinical evidence that the combination of INO (and/or sildenafil) and an inhaled prostacyclin provide greater pulmonary vasodilation than either used alone, by simultaneously activating cGMP and cAMP.[16,17] Prostacyclin impedes platelet aggregation and could promote bleeding but this concern appears to be more theoretic than real.

Epoprostenol

Epoprostenol (Flolan®) is a short-acting prostacyclin that is approved for continuous IV infusion for in patients with PAH. However, IV infusion causes as much systemic as pulmonary vasodilation, which is poorly tolerated in the perioperative period, especially when there is concomitant vasodilatory shock. In the blood, epoprostenol undergoes rapid spontaneous hydrolysis (t½ 2-3 min) to 6-keto-prostaglandin F1α. Administration by inhalation provides relatively selective, short-acting and titrateable pulmonary vasodilation and improved RV function.[18] A number of US centers administer (off-label) inhaled epoprostenol via a syringe infusion pump coupled to a nebulizer, and by dilution with saline the dose is varied from 12.5 to 50 ng/kg/min.

Iloprost

Iloprost is a synthetic prostacyclin analog that has a longer half-life (20-30 min) and is approved for administration by a metered dose inhaler, given at a dose of 2.5-5 mcg every 2-4 hrs. The device can easily be adapted for connection to an endotracheal or tracheostomy tube. Iloprost is approved for the treatment of PAH, but is used off label to treat acutely elevated PVR after cardiac surgery and lung transplantation.

Compared to epoprostenol, iloprost's primary limitation is the need for repetitive inhalations every 2-4 hrs. It has slower onset and offset than INO and it is not immediately inactivated, undergoing biotransformation in the liver. Thus, there is some potential for systemic vasodilation and hypotension. The advantages of iloprost are that it is much less expensive than INO, has no toxic metabolites and there is little if any risk of rebound pulmonary hypertension. In the intraoperative and early postoperative periods, INO may be preferable because of its rapid onset and titrateability and lack of systemic hypotensive effects. However, when they are more hemodynamically stable patients can be easily transitioned to inhaled Iloprost, which provides an effective means of weaning INO, avoiding rebound pulmonary hypertension, and continuing pulmonary vasodilation after tracheal extubation.

A third analog, trepostinil, has a longer duration of action than iloprost,[19] but has not been adapted for use in the perioperative period.

Inhaled Prostacyclin vs. INO

Inhaled PGI_2 was compared to inhaled nitric oxide in a prospective, randomized cross-over trial for the treatment of pulmonary hypertension following heart or lung transplantation.[20] Both agents were effective in decreasing PVR, pulmonary artery pressure and right atrial pressure, and improved cardiac index and mixed venous oxygen saturation. There were no significant differences in these parameters after cross-over to the other agent. Neither medication affected systemic blood pressure.

Given their lower cost and lack of potential toxicity, inhaled prostacyclins should be considered as primary or transitional therapy in the treatment of perioperative pulmonary hypertension.

Inhaled Milrinone

Milrinone is a selective PDE III inhibitor that results in the intracellular accumulation of cAMP. In myocardium this enhances inotropy, whereas in smooth muscle it promotes vasodilation (inodilation). The pulmonary vasodilator effects of milrinone are limited by systemic vasodilation, requiring the concomitant use of vasopressors such as norepinephrine and arginine vasopressin (see next section).

There are a some reports of a beneficial effect of administration of inhaled milrinone by ultrasonic nebulization, resulting in much more specific pulmonary vasodilation and decrease in elevated PVR.[21] The combination of inhaled prostacyclin and inhaled milrinone appears to have an additive effect on decreasing elevated PVR, presumably through an action in stimulating cAMP formation and preventing its breakdown that is analogous to combining INO and sildenafil.[22]

VASODILATORY SHOCK AND VASOPRESSOR THERAPY

Vasopressin and its Analogues

Arginine vasopressin (AVP) is a nonapeptide produced in the paraventricular and supraoptic nuclei of hypothalamus as a prohormone, cleaved to AVP and stored in secretory vesicles in the posterior pituitary.[23] AVP has a plasma half-life of 6-20 min and is rapidly metabolized by vasopressinases in the liver and kidney. Vasopressin receptors, sites of action and actions are summarized in Table 1.

Increased serum osmolality (> 1%), generates plasma AVP levels of 1-5 pg/mL that act on V_2 receptors, inducing an antidiuresis. Severe hypotension generates plasma AVP levels of 10-100 pg/mL that act on V_1 (formerly called V_{1a}) receptors, inducing peripheral vasoconstriction as a component of the baroreflex response. Activation of V_3 (V_{1b}) receptors induces ACTH and insulin release and may reflect the relationship

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

between AVP and glucocorticoid metabolism (see below). At high levels, AVP may activate purinergic (P2) receptors in the cardiac endothelium, inducing coronary vasoconstriction.[23] Oxytocin is a nonapeptide that differs from AVP by only two amino acids, yet its actions are very different (uterine contraction, milk let-down) and there is little cross-reactivity.

Table 1: Receptors, Sites of Action and Actions of Endogenous Vasopressin (AVP)23

Receptor	Site of Action	Action
V1 (V1a)	vascular smooth muscle	vasoconstriction
V2	collecting duct of nephron	antidiuresis
V3 (V1b)	anterior pituitary, pancreas	ACTH, insulin release

Pathogenesis of vasodilatory shock:

Vasodilatory shock has multiple pathways for induction.[24] Contact activation with any foreign surface, e.g. CPB, ECMO, ventricular assist device (VAD) triggers Hageman (Factor XII) activation and simultaneously activates the intrinsic pathway of coagulation, fibrinolysis and the complement system. Severe sepsis or systemic inflammatory response syndrome (SIRS) cause massive activation of inducible nitric oxide synthase (iNOS) and release of endogenous nitric oxide (NO). Protracted intracellular acidosis opens potassium-dependent ATP (KATP) channels in cell membranes, which allows potassium egress and hyperpolarization of the cell membrane, inactivating calcium channels and inhibiting the vasoconstrictor response to catecholamines such as norepinephrine (NE) or epinephrine, a syndrome known as vasoplegia. There is considerable evidence that in protracted shock, there is depletion of endogenous AVP from posterior pituitary, so that plasma AVP declines to < 3 pg/mL25.

Actions, benefits and limitations of AVP infusion in vasodilatory shock:

Low dose AVP infusion (1-4 u/hr, or 0.015-0.067 u/min) has a number of potentially beneficial effects in vasodilatory shock24. AVP appears to inhibit activation of inducible nitric oxide. It binds to and closes KATP channels, restores membrane polarity and the vasoconstrictor response to catecholamines. Depleted endogenous AVP levels are restored: infusion of 1-4 u/hr achieves plasma AVP levels of 20-30 pg/mL.

These actions consistently result in increased blood pressure and decreased catecholamine requirement. Diminution of high-dose NE decreases pulmonary vascular resistance (PVR) and cardiac arrhythmias. Compared to NE, AVP preferentially induces efferent arteriolar constriction and thereby may enhance glomerular filtration rate (GFR) and renal function.

The 2008 Surviving Sepsis Campaign recommends that AVP infusion (0.03 u/min) may be added to NE (still recommended for initial therapy) if the mean arterial pressure (MAP) cannot be maintained above 65 mmHg.[26]

Infusion of AVP must always be via a central line because extravasation may cause intense cutaneous vasoconstriction and injury. At excessive doses (> 6 u/hr) especially in low flow states, AVP infusion may cause acral cyanosis and cutaneous necrosis, and at higher doses still it promotes mesenteric vasoconstriction (thus its erstwhile use in variceal bleeding), hepatic dysfunction and even coronary vasoconstriction.

Evidence basis for use of AVP and its analogues in vasodilatory shock

The most definitive randomized controlled study (RCT) performed on AVP thus far is the Vasopressin and Septic Shock Trial (VASST).[27] It was designed to test the hypothesis that low-dose AVP infusion (0.01-0.03 u/min or 0.6-1.8 u/hr) would decrease 28-day mortality among patients with septic shock who were being treated with NE 5-15mcg/min. In the 778 patients studied, there was no significant difference in mortality between the AVP and NE (35.4% vs. 39.3%). However, in patients with less severe septic shock (prospectively defined as requiring NE 5-14 mcg/min), there was a significant improvement in mortality with AVP over NE (26.5% vs. 35.7%, $p < 0.05$). It is possible that the lack of benefit in more severe septic shock (NE > 14 mcg/min) was due to an inadequate dose of AVP or late intervention.

Role of corticosteroids in vasodilatory shock

An retrospective analysis of the VASST study by its authors demonstrated that the concomitant administration of corticosteroids with AVP significantly decreased mortality (35.9% vs. 44.7%, $p = 0.03$), and increased plasma AVP levels by one to two thirds.[28] This further implicates the relationship between AVP and steroid metabolism, considering that V3 receptor activation increases ACTH release and cortisol levels. It also warrants future prospective studies.

Indeed, the role of steroids in septic shock remains in flux.[29] The use of ACTH-stimulation tests to evoke adrenal hyporesponsiveness as an indication for hydrocortisone therapy has been discredited by subsequent equivocal outcomes, intra-study use of etomidate (which impairs cortisol synthesis), and the observation that these studies were based upon total rather than free cortisol levels30. The 2008 Surviving Sepsis Campaign recommends the administration of hydrocortisone (≤ 300 mg/day) when hypotension responds poorly to adequate fluid resuscitation and vasopressors , and that it should be weaned once vasopressors are no longer required.[26]

Terlipressin

Terlipressin (tricyl-lysine vasopressin) is an AVP analogue used in Europe but not currently available in the US or Canada. It is twice as potent at the V1 receptor than AVP, but has a much more prolonged half-life (4-6 hr), which makes it more difficult to titrate.[23] A small European RCT (TERLIVAP) compared continuous infusion of AVP (0.03 u/min) and terlipressin (1.3 mcg/kg/hr) with NE (15 mcg/min) as first-line therapy in septic shock in 45 patients.[31] Terlipressin appeared

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

superior to AVP in decreasing NE requirements, with lower bilirubin levels and less rebound hypotension, but had a greater effect in lowering platelet count.

METHYLENE BLUE

Actions of methylene blue

Methylene blue appears to inhibit guanylate cyclase, the enzyme that catalyzes the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP), which mediates the vasodilator effect of NO. It may also cause selective inhibition of iNOS.

Evidence basis for use of methylene blue in vasodilatory shock

Anecdotal observations of the benefits of methylene blue (MB) in severe vasodilatory shock have been made for many years.[32,33]

Dosing has ranged between 1-4 mg/ kg given as a single dose infused over 30 min to 4 hrs. MB increases MAP and cardiac index (CI). The latter may be due to increase preload secondary to venoconstriction, or a decrease in the impact of high levels of NO, which is a myocardial depressant that impedes the inotropic effect of catecholamines. Arterial lactate decreases, but this may be in part from its effect as a reducing agent. However, PVR also increases and arterial oxygenation may decrease.[34,35] Although decreases in endogenous production of NO, interleukins and tumor necrosis factor (TNF) have not been noted,[36] urinary excretion of NO metabolites is substantially lower.[37] Attenuation of the urinary excretion of renal tubular injury markers has also been noted.

A small dose-ranging randomized control trial (RCT) on 15 patients evaluated MB at 1mg/kg, 3mg/kg or 7mg/kg over 20 min. The authors noted a dose-dependent enhancement of hemodynamic function even at the lowest dose, but cautioned that high doses of MB may compromise splanchnic perfusion.[38] In another small RCT of 20 patients with septic shock, patients were randomized to placebo or MB 2 mg/kg, followed two hrs later by increasing infusion rates between 0.25 and 2 mg/hr over 4 hrs.[39] The most striking finding was a 40-87% decrease in dose requirement for NE, epinephrine and dopamine.

In the largest postoperative RCT performed to date, the vasoplegic syndrome was defined as a combination of hypotension due to low SVR, low cardiac filling pressures, normal or high cardiac index, and high vasopressor requirement.[40] 56 of 638 consecutive cardiac surgery patients met criteria and were randomized to MB 1.5 mg/kg or placebo. Patients who received MB had a significantly shorter duration of vasoplegia (6 vs. > 48 hrs) and lower mortality (0% vs. 21.4%).

A novel approach was taken by Ozal et al., who administered MB 2 mg/kg over 30 min or placebo one hr preoperatively to 100 patients undergoing coronary revascularization who were at high risk for vasoplegic syndrome because they were on ACE inhibitors, calcium channel blockers or heparin.[41] Patients who received MB before surgery had a significant reduction in postoperative vasoplegia (0% vs. 26%), ICU and hospital LOS.

We have observed occasionally dramatic responses to MB 2 mg/kg administered over 30 min in severe vasoplegia.[42] However, because of its potential to increase PVR, in our practice we restrict its use to patients who are already receiving inhaled NO.

RENAL PROTECTION: BIOMARKERS AND PHARMACOLOGIC INTERVENTIONS

Biomarkers

Ischemic acute kidney injury (AKI) progresses through several phases (prerenal, initiation, extension, maintenance and recovery). The success of any intervention to restore GFR thus depends on its timing – the earlier, the better. However, traditional renal function tests do not allow early recognition of AKI. Development of robust, easily detectable and prompt biomarkers of renal injury might allow us to assess the site, duration, etiology, prognosis and course of renal injury, and the effect of prophylactic or therapeutic interventions.[43,44]

Serum Creatinine

Serum creatinine (SCr) is not a marker of renal injury, but of renal function, and reflects the balance between muscle creatinine production and renal excretion.[45] SCr is a useful marker of glomerular filtration rate (GFR) in a steady state, but it is important to appreciate that the relationship between SCr and GFR is inverse and exponential. A doubling of the serum creatinine implies a halving of the GFR. There are numerous limitations to SCr as a reflection of steady state GFR as well as of acute changes in GFR.

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

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

Importantly, it may take 2 to 7 days before the SCr reaches a new steady state that reflects acute changes in GFR. This explains why intraoperative AKI is so often reflected by a postoperative SCr that does not peak until 5-7 days after surgery. Indeed, after a transient renal insult (e.g. suprarenal aortic cross-clamping) SCr may increase for a few days while GFR is actually recovering.[46]

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

Cystatin C

Cystatin C is a cysteine-protease inhibitor that is released into the circulation by all nucleated cells. It is completely filtered by the glomerulus, reabsorbed and not secreted by the tubules; thus, increased serum cystatin C levels reflect decreased GFR, and increased urinary levels reflect tubular injury.[47] Elevation of urinary cystatin C within 6 hr of cardiac surgery has been shown to have a strong correlation with AKI defined by subsequent elevation of SCr48. Unlike creatinine, cystatin C levels are not affected by muscle mass, age or gender, and there is evidence that it more accurately tracks GFR and responds more quickly.[49,50] However, certain factors such as cigarette smoking, inflammation and immunosuppressive therapy do independently elevate cystatin C.[51]

Classic biomarkers of tubular injury

Beta-2 microglobulin (B2M) is a small protein component of the major histocompatibility complex that is present on the surface of almost all cells.[52] It is normally filtered by the glomerulus and then undergoes partial tubular reabsorption. The ratio of serum to urine B2M may help distinguish glomerular from tubular injury. In the former, serum B2M increases because it is not filtered. In the latter, urinary B2M increases because it is not reabsorbed.

Increased urinary concentration of the tubular enzyme, N-acetyl beta D-glucosaminidase (NAG) is an index of subclinical tubular injury.[53] Urinary NAG levels, or the ratio of its isoenzymes, is used in the early detection of rejection after renal transplantation. However, the relationship between tubular enzymuria and clinical AKI is not known.

New biomarkers of tubular injury

Neutrophil gelatinase-associated lipocalin (NGAL) is a small 25 kDA polypeptide expressed in proximal tubular cells. Within minutes after ischemic tubular injury NGAL expression is dramatically up-regulated - 3-4 fold within 2-3 hrs, and up to 10,000 fold by 24 hrs.[54] NGAL is readily detected by ELISA in tiny (micromililiter) amounts of urine almost immediately after renal injury, preceding the appearance of NAG and beta2-microglobulin.

Urinary NGAL increases significantly within two hr of CPB in pediatric or adult patients who subsequently go on to develop a 50% increase in postoperative SCr, whose peak is delayed until 2-5 days after surgery.[55] However, the sensitivity and specificity in individual patients is much greater in pediatric (AUC 0.98) than adult cardiac surgery (0.74).[56] This may be explained by pediatric patients having a single insult imposed upon previously normal renal function, whereas, adults have varying preoperative GFR and co-morbidity, with multiple disparate renal insults. Thus although urinary NGAL may represent an early, sensitive, noninvasive urinary biomarker for ischemic and nephrotoxic AKI, it is not yet useful for management decisions in an individual patient.

Interleukin-18 (IL-18) is a pro-inflammatory cytokine that is involved in ischemic AKI. After CPB, urinary IL-18 is elevated within 4-6 hrs (i.e. later than NGAL), and levels may reflect the severity and duration of ischemic AKI.[57]

Kidney injury molecule-1 (KIM-1) is an immunoglobulin that normally resides in proximal renal tubular cells. After ischemic or nephrotoxic AKI, KIM-1 levels become dramatically elevated, perhaps because the protein plays a role in scavenging apoptotic and necrotic tubular cells.[58] However, compared with NGAL and IL-18, the levels of KIM-1 peak considerably later, at about 12-24 hrs.

Conclusions

Despite their promise, individual biomarkers of AKI have not yet replaced traditional markers in clinical and investigational studies. There is considerable interest in the development of a panel of early markers of acute tubular injury (NGAL, IL-18, KIM-1) together with a more reliable marker of GFR (cystatin C).[43] The hope is that these panels will be more useful for timing the initial insult and duration of AKI, and in predicting outcome (requirement for dialysis, mortality). Much work remains to be done to validate their sensitivity and specificity in large, diverse patient populations.

PHARMACOLOGIC PROTECTION

Osmotic and Loop Diuretics

Mannitol (25-50 g) is routinely added to the pump prime, although there are few clinical data that define its true role in renal protection during CPB. It does not prevent subclinical renal injury (microalbuminuria, tubular enzymuria), but AKI after uncomplicated CPB in patients with previously normal renal function is rare. Mannitol increases urine flow during infra-renal cross-clamping but does not prevent intraoperative decreases in GFR Postoperative osmotic diuresis can exacerbate hypovolemia and hypokalemia; persistent isosthenuria actually is predictive of CPB-induced tubular injury.

Loop diuretics (furosemide, bumetanide, torsemide, ethacrynic acid) have long been used to "convert" oliguric to nonoliguric AKI. However, it is most likely that oliguric patients who respond to diuretics have a lesser renal injury than those who do not, with an intrinsically more favorable outcome. Once dialysis is required, high dose furosemide does not alter the natural history of AKI.

Dopaminergic Agonists

Dopaminergic agents (dopamine, fenoldopam) potentially confer renal protection by increasing renal blood flow (RBF), diuresis and saliuresis. By activating cyclic AMP they "turn off" the energy-dependent tubular sodium pump and thereby decrease tubular oxygen consumption; increased intratubular urine flow protects against tubular obstruction.

Low dose (1-3 µg/kg/min) dopamine, added to high dose furosemide and mannitol, can also convert oliguric to nonoliguric states if given within a few hours of injury. However there is little evidence that

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

"prophylactic" low dose dopamine has any role in cardiac surgery. In part this may be because there is very wide variability in dopamine pharmacokinetics, i.e. some patients given low dose dopamine may achieve high plasma levels, i.e. in the beta- or alpha-adrenergic range.[59] When oliguria is associated with slow heart rate and low blood pressure in a volume repleted patient, initiation of dopamine as an inotropic agent can be very helpful. However, its usefulness is limited by its propensity to induce supraventricular arrhythmias especially postoperative atrial fibrillation.[60]

Fenoldopam is a phenol derivative of dopamine that is selective for the DA-1 receptor and lacks any beta- or alpha-adrenergic effects. There is increasing evidence that prophylactic perioperative administration at low doses (0.5-1.0 mcg/kg/min) can preserve GFR during and after CPB and decrease the requirement for postoperative dialysis.[61,62]

Natriuretic Peptides

The natriuretic peptides are formed by the endogenous synthesis of chains of 22-32 amino acids. They specifically oppose the sympathoadrenal, renin-angiotensin, aldosterone, and arginine vasopressin (AVP) systems, and induce vasodilation and natriuresis via activation of cyclic GMP. A-type (atrial) natriuretic peptide (ANP) is released by atrial stretch; B-type (brain) natriuretic peptide (BNP) is released by ventricular dilation. Assay of BNP (and its precursor, N-terminal-pro-BNP) is an established diagnostic tool for acute cardiac failure.[63] C-type natriuretic peptide (CNP, great vessels) and urodilatin (kidney) are endogenous analogs.

Human recombinant ANP (anaritide) infusion during CPB significantly decreases renin-angiotensin and aldosterone responses, and preserves GFR. Preliminary data suggested that administration in patients with severe AKI it could decrease dialysis requirement and mortality.[64] However, mortality was increased in nonoliguric patients, perhaps because the surviving nephrons are more sensitive to hypotension induced by ANP. A subsequent trial in oliguric patients showed no difference in outcome.[65]

Human Recombinant BNP (nesiritide) is FDA-approved for the parenteral treatment of patients with advanced decompensated CHF (ADCHF). Infusion decreases cardiac preload and afterload, promotes diuresis and relieves pulmonary edema and anasarca. Considerable controversy has been elicited by implications that nesiritide may adversely affect renal function in ADCHF.[66] However, in a prospective, controlled study in patients undergoing coronary revascularization of mitral valve surgery with CPB, a perioperative infusion of nesiritide (0.01 mcg/kg/min) was associated with lower SCr and 6-month mortality.[67]

N-Acetylcysteine

N-acetylcysteine (NAC) is naturally occurring glutathione precursor and free radical scavenger. It is well established in the treatment of acetaminophen toxicity, and there is considerable experimental evidence of its effectiveness in ameliorating nephrotoxic AKI. When combined with hydration, prophylactic oral NAC (600 mg PO bid x 2 days) provides significant renal protection in radiocontrast nephropathy (RCN).[68,69] However, NAC may decrease creatinine production and thereby give a false impression of the extent of its benefit.[70]

No renal benefit has been demonstrated by the perioperative infusion of NAC during cardiac surgery.[71] NAC must pass through the liver to be converted to glutathione, so in part this may be due to inadequate knowledge regarding the appropriate parenteral dose of NAC to protect against clinical IRI.[72]

Sodium Bicarbonate

It is well established that urinary alkalinization (pH > 6.5) protects against tubular injury in myoglobinuria (rhabdomyolysis) as well as RCN. There is now preliminary clinical evidence that urinary alkalinization might ameliorate AKI during cardiac surgery,[73] although an accompanying editorial in the same journal urged caution in interpreting the results of this pilot study.[74]

REFERENCES

1. Takayama H, Worku B, Naka Y. Postoperative management of the patient with a ventricular assist device. In: Sladen RN, ed. Postoperative Cardiac Care A Society of Cardiovascular Anesthesiologists Monograph Baltimore: Lippincott Williams & Wilkins; 2011: 191-206.
2. Dang NC, Topkara VK, Mercando M, et al. Right heart failure after left ventricular assist device implantation in patients with chronic congestive heart failure. J Heart Lung Transplant 2006;25:1-6.
3. Royster RL, Butterworth JFt, Prielipp RC, et al. Combined inotropic effects of amrinone and epinephrine after cardiopulmonary bypass in humans. Anesth Analg 1993;77:662-72.
4. Toller WG, Stranz C. Levosimendan, a new inotropic and vasodilator agent. Anesthesiology 2006;104:556-69.
5. De Hert SG, Lorsomradee S, Cromheecke S, Van der Linden PJ. The effects of levosimendan in cardiac surgery patients with poor left ventricular function. Anesth Analg 2007;104:766-73.
6. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med 2001;345:1435-43.
7. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med 2009;361:2241-51.
8. Morshuis M, Schoenbrodt M, Nojiri C, et al. DuraHeart magnetically levitated centrifugal left ventricular assist system for advanced heart failure patients. Expert Rev Med Devices 2010;7:173-83.
9. Hill NS, Roberts KR, Preston IR. Postoperative pulmonary hypertension: etiology and treatment of a dangerous complication. Respir Care 2009;54:958-68.
10. Haddad F, Couture P, Tousignant C, Denault AY. The right ventricle in cardiac surgery, a perioperative perspective: II. Pathophysiology, clinical importance, and management. Anesth Analg 2009;108:422-33.
11. Bertolissi M, Bassi F, Da Broi U. Norepinephrine can be useful for the treatment of right ventricular failure combined with acute pulmonary hypertension and systemic hypotension. A case report. Minerva Anestesiol 2001;67:79-84.
12. Inglessis I, Shin JT, Lepore JJ, et al. Hemodynamic effects of inhaled nitric oxide in right ventricular myocardial infarction and cardiogenic shock. J Am Coll Cardiol 2004;44:793-8.
13. Semigran MJ, Cockrill BA, Kacmarek R, et al. Hemodynamic effects of inhaled nitric oxide in heart failure. J Am Coll Cardiol 1994;24:982-8.
14. Manktelow C, Bigatello LM, Hess D, Hurford WE. Physiologic determinants of the response to inhaled nitric oxide in patients with acute respiratory distress syndrome. Anesthesiology 1997;87:297-307.

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

15. Vachiery J-L, Huez S, Gillies H, et al. Safety, tolerability and pharmacokinetics of an intravenous bolus of sildenafil in patients with pulmonary arterial hypertension. British Journal of Clinical Pharmacology 2011;71:289-92.
16. Hill LL, Pearl RG. Combined inhaled nitric oxide and inhaled prostacyclin during experimental chronic pulmonary hypertension. J Appl Physiol 1999;86:1160-4.
17. Miyaji K, Nagata N, Miyamoto T, Kitahori K. Combined therapy with inhaled nitric oxide and intravenous epoprostenol (prostacyclin) for critical pulmonary perfusion after the Fontan procedure. J Thorac Cardiovasc Surg 2003;125:437-9.
18. Hache M, Denault A, Belisle S, et al. Inhaled epoprostenol (prostacyclin) and pulmonary hypertension before cardiac surgery. J Thorac Cardiovasc Surg 2003;125:642-9.
19. Voswinckel R, Enke B, Reichenberger F, et al. Favorable effects of inhaled treprostinil in severe pulmonary hypertension: results from randomized controlled pilot studies. J Am Coll Cardiol 2006;48:1672-81.
20. Khan TA, Schnickel G, Ross D, et al. A prospective, randomized, crossover pilot study of inhaled nitric oxide versus inhaled prostacyclin in heart transplant and lung transplant recipients. J Thorac Cardiovasc Surg 2009;138:1417-24.
21. Denault AY, Lamarche Y, Couture P, et al. Inhaled milrinone: a new alternative in cardiac surgery? Semin Cardiothorac Vasc Anesth 2006;10:346-60.
22. Haraldsson Ö, Kieler-Jensen N, Ricksten S-E. The additive pulmonary vasodilatory effects of inhaled prostacyclin and inhaled milrinone in postcardiac surgical patients with pulmonary hypertension. Anesthesia & Analgesia 2001;93:1439-45.
23. Favory R, Salgado DR, Vincent JL. Investigational vasopressin receptor modulators in the pipeline. Expert Opin Investig Drugs 2009;18:1119-31.
24. Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. N Engl J Med 2001;345:588-95.
25. Landry DW, Levin HR, Gallant EM, et al. Vasopressin deficiency contributes to the vasodilation of septic shock. Circulation 1997;95:1122-5.
26. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36:296-327.
27. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med 2008;358:877-87.
28. Russell JA, Walley KR, Gordon AC, et al. Interaction of vasopressin infusion, corticosteroid treatment, and mortality of septic shock. Crit Care Med 2009;37:811-8.
29. Sprung CL, Goodman S, Weiss YG. Steroid therapy of septic shock. Crit Care Clin 2009;25:825-34, x.
30. Hamrahian AH, Oseni TS, Arafah BM. Measurements of serum free cortisol in critically ill patients. N Engl J Med 2004;350:1629-38.
31. Morelli A, Ertmer C, Rehberg S, et al. Continuous terlipressin versus vasopressin infusion in septic shock (TERLIVAP): a randomized, controlled pilot study. Crit Care 2009;13:R130.
32. Daemen-Gubbels CR, Groeneveld PH, Groeneveld AB, van Kamp GJ, Bronsveld W, Thijs LG. Methylene blue increases myocardial function in septic shock. Crit Care Med 1995;23:1363-70.
33. Preiser JC, Lejeune P, Roman A, et al. Methylene blue administration in septic shock: a clinical trial. Crit Care Med 1995;23:259-64.
34. Gachot B, Bedos JP, Veber B, Wolff M, Regnier B. Short-term effects of methylene blue on hemodynamics and gas exchange in humans with septic shock. Intensive Care Med 1995;21:1027-31.
35. Weingartner R, Oliveira E, Oliveira ES, et al. Blockade of the action of nitric oxide in human septic shock increases systemic vascular resistance and has detrimental effects on pulmonary function after a short infusion of methylene blue. Braz J Med Biol Res 1999;32:1505-13.
36. Park BK, Shim TS, Lim CM, et al. The effects of methylene blue on hemodynamic parameters and cytokine levels in refractory septic shock. Korean J Intern Med 2005;20:123-8.
37. Heemskerk S, van Haren FM, Foudraine NA, et al. Short-term beneficial effects of methylene blue on kidney damage in septic shock patients. Intensive Care Med 2008;34:350-4.
38. Juffermans NP, Vervloet MG, Daemen-Gubbels CR, Binnekade JM, Jong MD, Groeneveld AB. A dose-finding study of methylene blue to inhibit nitric oxide actions in the hemodynamics of human septic shock. Nitric Oxide 2010.
39. Kirov MY, Evgenov OV, Evgenov NV, et al. Infusion of methylene blue in human septic shock: a pilot, randomized, controlled study. Critical care medicine 2001;29:1860-7.
40. Levin RL, Degrange MA, Bruno GF, et al. Methylene blue reduces mortality and morbidity in vasoplegic patients after cardiac surgery. Ann Thorac Surg 2004;77:496-9.
41. Ozal E, Kuralay E, Yildirim V, et al. Preoperative methylene blue administration in patients at high risk for vasoplegic syndrome during cardiac surgery. Ann Thorac Surg 2005;79:1615-9.
42. Flynn BC, Sladen RN. The use of methylene blue for vasodilatory shock in a pediatric lung transplant patient. J Cardiothorac Vasc Anesth 2009;23:529-30.
43. Parikh CR, Devarajan P. New biomarkers of acute kidney injury. Crit Care Med 2008;36:S159-65.
44. Han WK, Wagener G, Zhu Y, Wang S, Lee HT. Urinary biomarkers in the early detection of acute kidney injury after cardiac surgery. Clin J Am Soc Nephrol 2009;4:873-82.
45. Sladen RN. Renal physiology. . In: Miller RD, ed. Miller's Anesthesia. 7th ed. Philadelphia: Churchill Livingstone; 2010:441-76.
46. Myers BD, Miller DC, Mehigan JT, et a. Nature of the renal injury following total renal ischemia in man. Journal of Clinical Investigation 1984;73:329-41.
47. Uchida K, Gotoh A. Measurement of cystatin-C and creatinine in urine. Clinica chimica acta; international journal of clinical chemistry 2002;323:121-8.
48. Koyner JL, Bennett MR, Worcester EM, et al. Urinary cystatin C as an early biomarker of acute kidney injury following adult cardiothoracic surgery. Kidney international 2008;74:1059-69.
49. Hojs R, Bevc S, Ekart R, Gorenjak M, Puklavec L. Serum cystatin C as an endogenous marker of renal function in patients with mild to moderate impairment of kidney function. Nephrol Dial Transplant 2006;21:1855-62.
50. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. Am J Kidney Dis 2002;40:221-6.
51. Rule AD, Bergstralh EJ, Slezak JM, Bergert J, Larson TS. Glomerular filtration rate estimated by cystatin C among different clinical presentations. Kidney international 2006;69:399-405.
52. Canivet JL, Larbuisson R, Damas P, et al. Plasma renin activity and urine beta 2-microglobulin during and after cardiopulmonary bypass: pulsatile vs non-pulsatile perfusion. Eur Heart J 1990;11:1079-82.
53. Price RG. Urinary N-acetyl-beta-D-glucosaminidase (NAG) as an indicator of renal disease. Curr Probl Clin Biochem 1979:150-63.
54. Mishra J, Ma Q, Prada A, et al. Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. J Am Soc Nephrol 2003;14:2534-43.
55. Mishra J, Dent C, Tarabishi R, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet 2005;365:1231-8.
56. Wagener G, Gubitosa G, Wang S, Borregaard N, Kim M, Lee HT. Urinary neutrophil gelatinase-associated lipocalin and acute kidney injury after cardiac surgery. Am J Kidney Dis 2008;52:425-33.
57. Parikh CR, Abraham E, Ancukiewicz M, Edelstein CL. Urine IL-18 is an early diagnostic marker for acute kidney injury and predicts mortality in the intensive care unit. J Am Soc Nephrol 2005;16:3046-52.
58. Han WK, Bailly V, Abichandani R, Thadhani R, Bonventre JV. Kidney Injury Molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. Kidney international 2002;62:237-44.
59. MacGregor DA, Smith TE, Prielipp RC, Butterworth JF, James RL, Scuderi PE. Pharmacokinetics of dopamine in healthy male subjects. Anesthesiology 2000;92:338-46.
60. Chiolero R, Borgeta A, Fisher A. Postoperative arrhythmias and risk factors after open heart surgery. Thoracic and Cardiovascular Surgeon 1991;39:81-4.
61. Landoni G, Biondi-Zoccai GG, Tumlin JA, et al. Beneficial impact of fenoldopam in critically ill patients with or at risk for acute renal failure: a meta-analysis of randomized clinical trials. Am J Kidney Dis 2007;49:56-68.
62. Cogliati AA, Vellutini R, Nardini A, et al. Fenoldopam infusion for renal protection in high-risk cardiac surgery patients: a randomized clinical study. J Cardiothorac Vasc Anesth 2007;21:847-50.
63. Baughman KL. B-type natriuretic peptide -- a window to the heart. N Engl J Med 2002;347:158-9.
64. Allgren RL, Marbury TC, Rahman SN, et al. Anaritide in acute tubular necrosis. Auriculin Anaritide Acute Renal Failure Study Group. N Engl J Med 1997;336:828-34.
65. Lewis J, Salem MM, Chertow GM, et al. Atrial natriuretic factor in oliguric acute renal failure. Anaritide Acute Renal Failure Study Group. Am J Kidney Dis 2000;36:767-74.
66. Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. Circulation 2005;111:1487-91.

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

67. Mentzer RM, Jr., Oz MC, Sladen RN, et al. Effects of perioperative nesiritide in patients with left ventricular dysfunction undergoing cardiac surgery:the NAPA Trial. J Am Coll Cardiol 2007;49:716-26.

68. Marenzi G, Assanelli E, Marana I, et al. N-acetylcysteine and contrast-induced nephropathy in primary angioplasty. N Engl J Med 2006;354:2773-82.

69. Tepel M, van der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. N Engl J Med 2000;343:180-4.

70. Hoffmann U, Fischereder M, Kruger B, Drobnik W, Kramer BK. The value of N-acetylcysteine in the prevention of radiocontrast agent-induced nephropathy seems questionable. J Am Soc Nephrol 2004;15:407-10.

71. Burns KE, Chu MW, Novick RJ, et al. Perioperative N-acetylcysteine to prevent renal dysfunction in high-risk patients undergoing cabg surgery: a randomized controlled trial. Jama 2005;294:342-50.

72. Shalansky SJ, Pate GE, Levin A, Webb JG. N-acetylcysteine for prevention of radiocontrast induced nephrotoxicity: the importance of dose and route of administration. Heart 2005;91:997-9.

73. Haase M, Haase-Fielitz A, Bellomo R, et al. Sodium bicarbonate to prevent increases in serum creatinine after cardiac surgery: a pilot double-blind, randomized controlled trial. Crit Care Med 2009;37:39-47.

74. Weisberg LS. Sodium bicarbonate for renal protection after heart surgery: Let's wait and see. Crit Care Med 2009;37:333-4.

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

Obstetric Anesthesia Update: The New Decade

Cynthia A. Wong, MD
Professor and Vice Chair
Northwestern University Feinberg School of Medicine
Section Chief, Obstetric Anesthesiology, Chicago, IL 60611 USA

OBJECTIVES:

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

- Understand current knowledge regarding use of oxytocin for postpartum hemorrhage prophylaxis, including dose and side effects.
- Understand current knowledge regarding treatment of postdural puncture headache after unintentional dural puncture.
- Explain the reasoning behind choice of vasopressors (ephedrine and phenylephrine) for the treatment of neuraxial-anesthesia induced hypotension during cesarean delivery.
- Understand the benefits and limits of crystalloid and colloid administration for the prevention of hypotension during spinal anesthesia for cesarean delivery.
- Understand current knowledge regarding risk of neuraxial infections associated with neuraxial procedures, and recommended techniques to minimize the risk of infection.
- Understand current evidence regarding neuraxial anesthesia/analgesia for external cephalic version of breech presentation.

OXYTOCIN FOR POSTPARTUM HEMORRHAGE PROPHYLAXIS

Recent studies of oxytocin for the management of the third stage of labor have focused on the adverse side effects of oxytocin and the appropriate dose. Oxytocin administered as a bolus (5 or 10 IU) is associated with transient hypotension, as well as ST-segment depression, and occasionally chest pain and shortness of breath.[1-3] Carvalho et al.[4] used a biased coin up-down sequential allocation technique to estimate the ED_{90} of oxytocin administered as a bolus to patients undergoing elective cesarean delivery. The primary outcome was satisfactory uterine tone as assessed by the obstetrician. The ED_{90} was 0.35 IU (95% CI 0.18 – 0.52). Butwick et al.[5] used a random dose allocation method (0, 0.5, 1, 3, 5 IU) to estimate the ED_{50} and ED_{95} of oxytocin in the same patient population. They were unable to estimate these values because of high prevalence of satisfactory uterine tone after all doses of oxytocin, including placebo. The highest dose (5 IU) was associated with a greater incidence of hypotension. Given these results, the investigators stated that high doses of oxytocin should no longer be given and recommend doses between 0.5 and 3 IU.

In an *in vitro* model using rat myometrium, pretreatment of the muscle strips with oxytocin increased the amount of oxytocin required for myometrial contraction in a concentration-dependent manner.[6] Similarly, the ED_{90} for oxytocin [2.99 IU (95% CI 2.32 – 3.67)] was higher in women who underwent cesarean delivery for arrest of labor who had been exposed to oxytocin during labor compared to the ED_{90} without prior exposure to oxytocin.[7]

In the United States, oxytocin administered as part of active management of the third stage of labor is most often administered as an *infusion*, not a bolus. George et al.[8] used a biased-coin up-down sequential allocation technique to estimate the ED_{90} of an oxytocin infusion. The primary outcome was satisfactory uterine tone 3 minutes after delivery as assessed by the obstetrician. The ED_{90} was 0.29 IU/min (95% CI 0.15 – 0.43). If one uses the upper end of the 95% confidence interval, the ED_{90} for an oxytocin infusion is approximately 25 IU/h.

In summary, recent studies suggest high dose oxytocin results in significant hypotension and ST-segment depression. High bolus doses (> 5 IU) are not indicated. Women with previous exposure to oxytocin during labor may require higher doses than those without prior exposure.

PREVENTION OF POSTDURAL PUNCTURE HEADACHE AFTER UNINTENTIONAL DURAL PUNCTURE

The incidence of unintentional dural puncture with an epidural needle during neuraxial procedures in obstetric patients is about 1.5%, and the incidence of postdural puncture headache (PDPH) after unintentional dural puncture is approximately 52%.[9] Techniques to prevent PDPH after dural puncture would be welcome. A recent meta-analysis of possible techniques in the general patient population (including obstetrics) has been published.[10]

Several studies have assessed whether a prophylactic blood patch decreases the incidence of PDPH,[11-14] although most of the studies have methodologic concerns. After unintentional dural puncture, an epidural catheter is placed and used for analgesia/anesthesia. After delivery, autologous blood is injected into the catheter, and the catheter is removed. Scavone et al.[14] performed a double-blind trial in parturients (n = 64) with unintentional dural puncture with a 17-gauge Tuohy needle. Twenty milliliter autologous blood was injected through the epidural catheter after delivery. There was no difference in the incidence of PDPH between the treatment and sham groups (56% in each group, 95% CI of difference (-25% to +25%), nor in the need for therapeutic blood patch (44% vs. 28%, 95% CI of difference -10% to 39%; P = 0.08).

A number of retrospective studies have assessed whether the presence of an intrathecal catheter decreases the risk of PDPH. In this technique, an intrathecal

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

catheter is threaded through the dural puncture after unintentional dura puncture, and used of analgesia/anesthesia. It is hypothesized that the presence of the catheter in the dural rent initiates an inflammatory reaction, resulting in faster healing. In a retrospective study, the incidence of PDPH was reduced from 81% in the control group (no intrathecal catheter) to 31% if the intrathecal catheter was removed after delivery and 3% if the intrathecal catheter was removed after 24 hours.[15] However, this study suffers from a number of methodologic flaws. Other observational studies have not found that the presence of an intrathecal catheter is protective for the development of PDPH, nor did a meta-analysis (RR 0.21, 95% CI 0.02 – 2.65).[10]

Two single-institution randomized controlled trials have assessed the efficacy of epidural morphine (3 mg shortly after delivery and 24 h later)[16] and intravenous cosyntropin (1 mg)[17] for the prevention of PDPH. Both techniques reduced the incidence of PDPH. However, neither study was powered to address side effects; larger studies are needed to confirm safety before these techniques can be recommended.

In summary, the best technique for avoiding PDPH is avoiding dural puncture with a large-bore needle. Evidence is currently not available to support use of specific interventions to avoid PDPH once dural puncture occurs.

EPHEDRINE VS. PHENYLEPHRINE FOR SPINAL ANESTHESIA-INDUCED HYPOTENSION

Ephedrine was the drug of choice for the treatment of hypotension during neuraxial anesthesia for cesarean delivery for many years. Studies in pregnant ewes suggested that ephedrine better maintained uterine blood flow compared to direct acting alpha-adrenergic agonists.[18] Recent evidence, however, no longer supports this practice. A number of human studies in the last 15 years have demonstrated that phenylephrine is equally effective for treating maternal hypotension. More importantly, in studies of spinal anesthesia for elective cesarean delivery, fetal acid-base status is actually improved with phenylephrine compared to ephedrine. A meta-analysis found no differences in maternal blood pressure, although bradycardia was more likely after phenylephrine treatment.[19] Umbilical artery pH was higher after treatment with phenylephrine (weighted mean difference of 0.03; 95% CI, 0.02-0.04), however there was no difference in the number of neonates with umbilical artery pH < 7.2 (RR 0.78; 95% CI, 0.16-3.92) or Apgar score < 7 at 1 and 5 min.

The adverse effect of ephedrine compared to phenylephrine on fetal pH is likely a direct effect of ephedrine on the fetus (increased fetal metabolic activity).[20] Ngan Kee et al.[21] found an increased rate of placental transfer of ephedrine vs. phenylephrine, as well as a decreased rate of fetal metabolism. It is unlikely that these drugs have any clinically significant adverse effect on the healthy fetus. It is unclear whether there is an adverse effect on fetuses with decreased reserve (e.g., intrauterine growth restriction, non-reassuring fetal status during labor).

Maintaining maternal blood pressure close to baseline decreases the incidence of fetal acidosis and maternal nausea and vomiting. Initiation of spinal anesthesia results in an acute decrease in systemic vascular resistance (SVR) and an increase in cardiac output (CO).[3,22] Phenylephrine treats the decrease in SVR and prevents the increase in CO and heart rate. There is no advantage to combining ephedrine and phenylephrine in terms of blood pressure control.[23] Two recent dose-response studies of prophylactic phenylephrine infusions to prevent hypotension after induction of spinal anesthesia in elective cesarean delivery patients concluded that there is no advantage of high dose infusion rates (75 – 100 µg/min) compared to lower rates (25 – 50 µg/min) for blood pressure control, number of interventions necessary to maintain blood pressure or fetal outcome.[24,25] Higher infusion rates are associated with a higher total drug dose.

CRYSTALLOID AND COLLOID ADMINISTRATION TO PREVENT HYPOTENSION DURING SPINAL ANESTHESIA

Factors associated with an increased risk for hypotension after spinal anesthesia include dose of local anesthesia (and maximum cephalad extent of blockade), low baseline blood pressure, high interspinous level of dural puncture, lack of labor (e.g., elective procedure), and increased baseline sympathetic tone.[26] Traditional preloading with crystalloid prior to the induction of spinal or epidural anesthesia does not significantly decrease the incidence of hypotension. In the presence of euvolemia, crystalloid solution is rapidly redistribution from the intravascular to interstitial space.[27] This may explain the ineffectiveness of preload (administered *prior* to the initiation of anesthesia, when the patient is euvolemic) in preventing hypotension. Dyer and colleagues[28] hypothesized that crystalloid administration may be more effective when administered immediately following the initiation of spinal anesthesia (termed coload), during the development of relative hypovolemia. Indeed, the incidence of hypotension was lower and need for ephedrine less, in a group of parturients randomized to coload (20 mL/kg) compared to a preload 20 min prior to induction.

Several groups of investigators have compared crystalloid preload to colloid (starch) preload and found that the incidence of hypotension after induction of spinal anesthesia is lower after colloid preload.[29-31] This conclusion is supported by a meta-analysis.[32] Several randomized controlled trials have compared colloid preload to colloid coload, and found no advantage of colloid preload compared to coload.[33,34] In any case, without the use of vasopressors, the incidence of hypotension remains greater than 20%, despite use of colloids or manipulation of timing of fluid administration.[32]

Ngan Kee[35] demonstrated that the combination of crystalloid coload with a prophylactic phenylephrine

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

infusion decreased the incidence of hypotension to 1.9% (95% CI 0.3-9.9%) compared to a group who received minimal fluids with phenylephrine (28.3% (95% CI 18.0 to 41.6%)).

Colloid is expensive, and some patients may have an allergic reaction. Whether routine colloid administration to all healthy women undergoing spinal anesthesia will contribute to improved outcomes is questionable; however, its use may be justified in women at increased risk of hypotension, or in women for whom hypotension or decrease in preload may be associated with clinically adverse outcomes. Taken together, these studies suggest that crystalloid should be administered rapidly at the time of induction of spinal anesthesia, and the use of colloid should be considered in women considered at high risk for hypotension.

NEURAXIAL ANESTHESIA-ASSOCIATED INFECTIONS

Spinal-epidural abscesses and meningitis are rare complications of neuraxial procedures. In a review of 38 case reports of postpartum meningitis, Reynolds[36] concluded that all cases were associated with neuraxial procedures (no cases occurred in the absence of a neuraxial procedure). Although there is no denominator, review of the reports suggests that labor and dural puncture are risk factors for meningitis.

In contrast to community acquired meningitis, iatrogenic meningitis is usually caused by streptococcal viridans species;[36] these organisms are commonly found in the upper airway. Case reports of meningitis following lumbar puncture procedures tend to occur in clusters rather than sporadically, and the offending bacteria have been linked to identical organisms in the airway of the proceduralist.[37] This suggests that meningitis is due to a break in sterile technique, and is not secondary to hematogenous spread.

Of significant concern is the January 2010 report by the Centers for Disease Control (CDC) of 5 obstetric patients in whom spinal or combined spinal-epidural labor analgesia was complicated by postpartum meningitis.[38] Three procedures from one hospital were linked to a single anesthesiologist, and 2 from a second hospital were linked to a second anesthesiologist. *Streptococcus salivarius* was the confirmed cause in 4 of the cases. One patient died. The CDC concluded that *S. salivarius* was likely transmitted directly from the anesthesiologist to the patients, either by droplet transmission directly from the oropharynx (one anesthesiologist did not wear a mask during the procedure), or contamination of sterile equipment. The CDC,[39] the American Society of Regional Anesthesia and Pain Medicine (ASRA),[40] and the American Society of Anesthesiologists (ASA)[41] all recommend that practitioners wear masks while performing neuraxial procedures.

In contrast to meningitis, epidural abscesses are more likely to be caused by skin flora (e.g., *Staph aureus*). Studies have suggested that chlorhexidine[42] and povidone iodine with alcohol[43] produce better skin antisepsis than povidone iodine. The ASRA,[40] the ASA,[41] and the Association of Anaesthetists of Great Britain and Ireland (AAGBI)[44] recommend an alcohol based chlorhexidine solution be used for skin asepsis before regional nerve block procedures. Other recommendations include removal of all jewelry (including rings and watches), handwashing with an alcohol-based antiseptic solution, sterile gloves, individual packets of antiseptics for skin preparation (not multidose bottles), sterile draping of the patient, and the use of sterile occlusive dressings.[40,41,44]

NEURAXIAL ANALGESIA/ANESTHESIA FOR EXTERNAL CEPHALIC VERSION OF BREECH PRESENTATION

A major indication for primary cesarean delivery is malpresentation. The American College of Obstetricians and Gynecologists (ACOG) states that the "cesarean delivery will be the preferred mode of delivery for most physicians because of the diminishing expertise in vaginal breech delivery."[45] However, the ACOG also states that "obstetricians should offer and perform external cephalic version whenever possible."[45] Successful external cephalic version (ECV) decreases the risk of cesarean delivery. A number of small randomized controlled trials have assessed whether neuraxial analgesia/anesthesia increases the likelihood of ECV compared to intravenous or no analgesia. The most recent trial in multiparous women found neuraxial anesthesia (bupivacaine 7.5 mg) resulted in improved success of ECV attempt compared to no analgesia (87 vs. 58%, 95% CI of difference 7.5% to 48%).[46] A meta-analysis (trials = 7, n = 681) also suggests that neuraxial anesthesia/analgesia may improve the rate of successful ECV compared to control (RR 1.44 (95% CI 1.16 – 1.79)).[47] The overall risk of adverse events was low and not different between groups. Several authors have noted that studies which employed *analgesic* doses of neuraxial local anesthetics had less favorable results compared to studies which employed *anesthetic* doses of local anesthetics.[47,48] A head-to-head comparison of neuraxial analgesia vs. anesthesia for ECV is warranted.

Given that the overall rate of cesarean delivery continues to climb, and that cesarean compared to vaginal delivery is associated with a higher incidence of morbidity and mortality, practices that improve the chance of successful ECV, and therefore decrease the rate of cesarean delivery, should be encouraged. A recent editorial by Caughey and El-Sayed[49] suggests that the evidence now supports offering neuraxial analgesia/anesthesia for this procedure.

REFERENCES

1. Jonsson M, Hanson U, Lidell C, Norden-Lindeberg S. ST depression at caesarean section and the relation to oxytocin dose. A randomised controlled trial. BJOG;117:76-83
2. Svanstrom MC, Biber B, Hanes M, Johansson G, Naslund U, Balfors EM. Signs of myocardial ischaemia after injection of oxytocin: a randomized double-blind comparison of oxytocin and methylergometrine during Caesarean section. Br J Anaesth 2008;100:683-9
3. Dyer RA, Reed AR, van Dyk D, Arcache MJ, Hodges O, Lombard CJ, Greenwood J, James MF. Hemodynamic effects of ephedrine, phenylephrine, and the coadministration of phenylephrine with oxytocin during spinal anesthesia for elective cesarean delivery. Anesthesiology 2009;111:753-65

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

4. Carvalho JC, Balki M, Kingdom J, Windrim R. Oxytocin requirements at elective cesarean delivery: a dose-finding study. Obstet Gynecol 2004;104:1005-10
5. Butwick AJ, Coleman L, Cohen SE, Riley ET, Carvalho B. Minimum effective bolus dose of oxytocin during elective Caesarean delivery. Br J Anaesth;104:338-43
6. Magalhaes JK, Carvalho JC, Parkes RK, Kingdom J, Li Y, Balki M. Oxytocin pretreatment decreases oxytocin-induced myometrial contractions in pregnant rats in a concentration-dependent but not time-dependent manner. Reprod Sci 2009;16:501-8
7. Balki M, Ronayne M, Davies S, Fallah S, Kingdom J, Windrim R, Carvalho JC. Minimum oxytocin dose requirement after cesarean delivery for labor arrest. Obstet Gynecol 2006;107:45-50
8. George RB, McKeen D, Chaplin AC, McLeod L. Up-down determination of the ED(90) of oxytocin infusions for the prevention of postpartum uterine atony in parturients undergoing Cesarean delivery. Can J Anaesth;57:578-82
9. Choi PT, Galinski SE, Takeuchi L, Lucas S, Tamayo C, Jadad AR. PDPH is a common complication of neuraxial blockade in parturients: a meta-analysis of obstetrical studies. Can J Anaesth 2003;50:460-9
10. Apfel CC, Saxena A, Cakmakkaya OS, Gaiser R, George E, Radke O. Prevention of postdural puncture headache after accidental dural puncture: a quantitative systematic review. Br J Anaesth;105:255-63
11. Ackerman WE, Colclough GW. Prophylactic epidural blood patch: the controversy continues [letter]. Anesth Analg 1987;66:913
12. Ackerman WE, Juneja MM, Kaczorowski DM. Prophylactic epidural blood patch for the prevention of postdural puncture headache in the parturient. Anesthesiol Rev 1990;17:45-9
13. Colonna-Romano P, Shapiro BE. Unintentional dural puncture and prophylactic epidural blood patch in obstetrics. Anesth Analg 1989;69:522-3
14. Scavone BM, Wong CA, Sullivan JT, Yaghmour E, Sherwani SS, McCarthy RJ. Efficacy of a prophylactic epidural blood patch in preventing post dural puncture headache in parturients after inadvertent dural puncture. Anesthesiology 2004;101:1422-7
15. Ayad S, Demian Y, S.N. N, Tetzlaff JE. Subarachnoid catheter placement after wet tap for analgesia in labor: Influence on the risk of headache in obstetric patients. Reg Anesth Pain Med 2003;28:512-5
16. Al-metwalli RR. Epidural morphine injections for prevention of post dural puncture headache. Anaesthesia 2008;63:847-50
17. Hakim SM. Cosyntropin for prophylaxis against postdural puncture headache after accidental dural puncture. Anesthesiology;113:413-20
18. Ralston DH, Shnider SM, DeLorimier AA. Effects of equipotent ephedrine, metaraminol, mephentermine, and methoxamine on uterine blood flow in the pregnant ewe. Anesthesiology 1974;40:354-70
19. Lee A, Ngan Kee WD, Gin T. A quantitative, systematic review of randomized controlled trials of ephedrine versus phenylephrine for the management of hypotension during spinal anesthesia for cesarean delivery. Anesth Analg 2002;94:920-6
20. Riley ET. Editorial I: Spinal anaesthesia for Caesarean delivery: keep the pressure up and don't spare the vasoconstrictors. Br J Anaesth 2004;92:459-61
21. Ngan Kee WD, Khaw KS, Tan PE, Ng FF, Karmakar MK. Placental transfer and fetal metabolic effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery. Anesthesiology 2009;111:506-12
22. Langesaeter E, Rosseland LA, Stubhaug A. Continuous invasive blood pressure and cardiac output monitoring during cesarean delivery: a randomized, double-blind comparison of low-dose versus high-dose spinal anesthesia with intravenous phenylephrine or placebo infusion. Anesthesiology 2008;109:856-63
23. Ngan Kee WD, Lee A, Khaw KS, Ng FF, Karmakar MK, Gin T. A randomized double-blinded comparison of phenylephrine and ephedrine infusion combinations to maintain blood pressure during spinal anesthesia for cesarean delivery: the effects on fetal acid-base status and hemodynamic control. Anesth Analg 2008;107:1295-302
24. Allen TK, George RB, White WD, Muir HA, Habib AS. A double-blind, placebo-controlled trial of four fixed rate infusion regimens of phenylephrine for hemodynamic support during spinal anesthesia for cesarean delivery. Anesth Analg;111:1221-9
25. Stewart A, Fernando R, McDonald S, Hignett R, Jones T, Columb M. The dose-dependent effects of phenylephrine for elective cesarean delivery under spinal anesthesia. Anesth Analg;111:1230-7
26. Hanss R, Bein B, Francksen H, Scherkl W, Bauer M, Doerges V, Steinfath M, Scholz J, Tonner PH. Heart rate variability-guided prophylactic treatment of severe hypotension after subarachnoid block for elective cesarean delivery. Anesthesiology 2006;104:635-43
27. Ueyama H, He YL, Tanigami H, Mashimo T, Yoshiya I. Effects of crystalloid and colloid preload on blood volume in the parturient undergoing spinal anesthesia for elective Cesarean section. Anesthesiology 1999;91:1571-6
28. Dyer RA, Farina Z, Joubert IA, Du Toit P, Meyer M, Torr G, Wells K, James MF. Crystalloid preload versus rapid crystalloid administration after induction of spinal anaesthesia (coload) for elective caesarean section. Anaesth Intensive Care 2004;32:351-7
29. Ko JS, Kim CS, Cho HS, Choi DH. A randomized trial of crystalloid versus colloid solution for prevention of hypotension during spinal or low-dose combined spinal-epidural anesthesia for elective cesarean delivery. Int J Obstet Anesth 2007;16:8-12
30. Dahlgren G, Granath F, Wessel H, Irestedt L. Prediction of hypotension during spinal anesthesia for Cesarean section and its relation to the effect of crystalloid or colloid preload. Int J Obstet Anesth 2007;16:128-34
31. Siddik SM, Aouad MT, Kai GE, Sfeir MM, Baraka AS. Hydroxyethylstarch 10% is superior to Ringer's solution for preloading before spinal anesthesia for Cesarean section. Can J Anaesth 2000;47:616-21
32. Morgan PJ, Halpern SH, Tarshis J. The effects of an increase of central blood volume before spinal anesthesia for cesarean delivery: a qualitative systematic review. Anesth Analg 2001;92:997-1005
33. Teoh WH, Sia AT. Colloid preload versus coload for spinal anesthesia for cesarean delivery: the effects on maternal cardiac output. Anesth Analg 2009;108:1592-8
34. Siddik-Sayyid SM, Nasr VG, Taha SK, Zbeide RA, Shehade JM, Al Alami AA, Mokadem FH, Abdallah FW, Baraka AS, Aouad MT. A randomized trial comparing colloid preload to coload during spinal anesthesia for elective cesarean delivery. Anesth Analg 2009;109:1219-24
35. Ngan Kee WD, Khaw KS, Ng FF. Prevention of hypotension during spinal anesthesia for cesarean delivery: an effective technique using combination phenylephrine infusion and crystalloid cohydration. Anesthesiology 2005;103:744-50
36. Reynolds F. Neurological infections after neuraxial anesthesia. Anesthesiology clinics 2008;26:23-52
37. Schneeberger PM, Janssen M, Voss A. Alpha-hemolytic streptococci: a major pathogen of iatrogenic meningitis following lumbar puncture. Case reports and a review of the literature. Infection 1996;24:29-33
38. Bacterial meningitis after intrapartum spinal anesthesia - New York and Ohio, 2008-2009. Mmwr 2010;59:65-9
39. Siegel J, Rhinehart E, Jackson M, Chiarello L. 2007 guidelines for isolation precautions: preventing transmission of infectious agents in healthcare settings. http://www.cdc.gov/ncidod/dhqp/gl_isolation.html.2007
40. Hebl JR. The importance and implications of aseptic techniques during regional anesthesia. Reg Anesth Pain Med 2006;31:311-23
41. American Society of Anesthesiologists Task Force on Infectious Complications Associated with Neuraxial Techniques. Practice advisory for the prevention, diagnosis, and management of infectious complications associated with neuraxial techniques: A report by the American Society of Anesthesiologists Task Force on Infectious Complications Associated with Neuraxial Techniques. Anesthesiology 2010;112
42. Kinirons B, Mimoz O, Lafendi L, Naas T, Meunier J, Nordmann P. Chlorhexidine versus povidone iodine in preventing colonization of continuous epidural catheters in children: a randomized, controlled trial. Anesthesiology 2001;94:239-44
43. Birnbach DJ, Meadows W, Stein DJ, Murray O, Thys DM, Sordillo EM. Comparison of povidone iodine and DuraPrep, an iodophor-in-isopropyl alcohol solution, for skin disinfection prior to epidural catheter insertion in parturients. Anesthesiology 2003;98:164-9
44. Infection control in anaesthesia. Anaesthesia 2008;63:1027-36
45. ACOG Committee Opinion No. 340. Mode of term singleton breech delivery. Obstet Gynecol 2006;108:235-7
46. Weiniger CF, Ginosar Y, Elchalal U, Sela HY, Weissman C, Ezra Y. Randomized controlled trial of external cephalic version in term multiparae with or without spinal analgesia. Br J Anaesth;104:613-8
47. Lavoie A, Guay J. Anesthetic dose neuraxial blockade increases the success rate of external fetal version: a meta-analysis. Can J Anaesth;57:408-14
48. Sullivan JT, Grobman WA, Bauchat JR, Scavone BM, Grouper S, McCarthy RJ, Wong CA. A randomized controlled trial of the effect of combined spinal-epidural analgesia on the success of external cephalic version for breech presentation. Int J Obstet Anesth 2009;18:328-34
49. Caughey AB, El-Sayed YY. Regional anesthesia for external cephalic version: its time has come. J Perinatol;30:569-70

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

Three-Dimensional Transesophageal Echocardiography: Pretty Pictures or an Advance in Technology

Stanton K. Shernan, MD, FAHA, FASE
Associate Professor of Anesthesiam, Chief, Division of Cardiac Anesthesia
Department of Anesthesiology, Brigham and Women's Hospital, Harvard School of Medicine

OBJECTIVES:

After attending this lecture, participants will understand:

1. the evolution of three-dimensional transesophageal echocardiography technology
2. current and future clinical applications of perioperative three-dimensional transesopha geal echocardiography

Although the concept of three-dimensional (3-D) echocardiography was first introduced in the early 1970s, its utility in the perioperative environment has only recently acquired appropriate recognition.[1] Advantages of both conventional 3-D reconstruction and real-time 3-D imaging (RT3-DE) techniques for enhancing the diagnostic confidence of conventional echocardiography in the perioperative period have begun to emerge in the literature.[2] Primary areas of interest have included the utility of 3-D echocardiography in preoperative surgical planning, *intraoperative* assessment of the surgical procedure, and postoperative early and long-term follow up to determine the need for further intervention.[3]

The utility of 3-D echocardiographic techniques in providing preoperative, noninvasive imaging of intracardiac lesions from the surgeon's visual perspective, has been demonstrated in patients with congenital heart and valvular lesions. Lange et al compared preoperative 2-D and 3-D TTE evaluations with intraoperative findings in 15 patients with atrioventricular septal defect morphology.[4] In comparison with preoperative 2-D echocardiography, 3-D TTE reconstruction provided superior imaging of the mitral valve (MV) and tricuspid valve function. In addition, 3-D TTE provided a more precise description of primum atrial septal defect (ASD) size, secundum ASD fenestrations and ventricular septal defect (VSD) size. Acar et al also performed pre-procedural 3-D TTE in 62 consecutive patients aged 2 to 18 years with ASDs scheduled for either transcatheter (n= 42) or surgical (n=20) closure.[5] Pre-procedural 3-D TTE measurement of ASD size correlated well with findings obtained intraoperatively and during transcatheter closure. A similar degree of accuracy for 3-D TTE evaluation of VSD size prior to closure has also been demonstrated.[6] Additional reported applications for preoperative 3-D echocardiography have included a complimentary role to conventional echocardiographic techniques in facilitating surgical planning for defining the shape, dimensions, location, origin, mobility and valve involvement of cardiac tumors.[7]

The accuracy, feasibility and value of 3-D echocardiography has also been demonstrated in the intraoperative environment.[8] Abraham et al performed intraoperative 2-D and 3-D reconstruction TEE examinations on 60 patients undergoing valve surgery.[9] In this study, 3-D acquisitions were completed in 87% of the patients within a mean acquisition time of 2.8 ± 0.2 minutes and reconstruction time within 8.6 ± 0.7 minutes. Three-D echocardiography detected all salient valve morphological pathology (leaflet perforations, fenestrations and masses) which was subsequently confirmed on pathological examination in 84% of the patients. In addition, intraoperative 3-D TEE provided new additional information not obtained by 2-D TEE in 15 patients (25%), and in 1 case influenced the surgeon's decision to perform a valve repair rather than a replacement. Furthermore, intraoperative 3-D reconstruction TEE provided worthwhile and complimentary anatomic information that explained the mechanism of valve dysfunction demonstrated by 2-D imaging and color flow Doppler. Ahmed et al evaluated the potential utility of 3-D TEE in identifying individual MV scallop prolapse in 36 adult patients with undergoing surgical correction.[10] Perfect correlation between 3-D TEE and surgical findings was noted in 78% of the patients. Similarly, De Castro et al demonstrated superior concordance between intraoperative 3-D TEE surgical identification of prolapsing anterior and posterior MV scallops compared to 2-D TEE.[11] Intraoperative 3-D TEE has also been used to identify distortion and folding of the mitral annulus as a cause of functional mitral stenosis or worsening mitral regurgitation during beating heart surgery while positioning to access the back of the heart.[12] For example, the superiority of intraoperative 3-D TEE compared to 2-D has been demonstrated in providing "en face" and oblique views of left atrioventricular (AV) valve septal malformations in patients undergoing reoperation for persistent regurgitant lesions after previous repair of partial AV septal defects.

The recent development and availability of RT3-DE has introduced additional opportunities for non-invasive diagnostic imaging to influence perioperative decision-making. Compared with conventional 3-D reconstruction, RT3-DE permits faster acquisition without a dependency on the electrocardiogram or respiratory gating, and allows simultaneous visualization of orthogonal planes with 2-D resolution. Disadvantages compared to conventional 2-D imaging include decreased line density in the acquired volume and slower frame rates. In addition, compared to conventional TEE probes, the larger dimensions of

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

RT3-DE transducers currently available for clinical utilization have limited their utilization to TTE or intraoperative epicardial viewing planes. Recently the introduction of more sophisticated miniaturized ultrasound transducers with real-time volume rendering capabilities has permitted the development of RT3-DE TEE which may be used intraoperatively to permit a more comprehensive evaluation to facilitate perioperative surgical planning.[13-26]

REFERENCES

1. Matsumoto M, Matsuo H, Kitabatake A, et al. Three-dimensional echocardiograms and two-dimensional echocardiographic images at desired planes by a computerized system. Ultrasound Med Biol 1977;3:163-178.
2. Hung J, Lang R, Flaschkampf F, Shernan S, et al. 3D echocardiography: a review of the current status and future directions. J Am Soc Echocardiogr. 2007 ;20:213-33.
3. Gunasegaran K, Yao J, De Castro S, Nesser H, Pandian N. Three-dimensional transesophageal echocardiography and other future directions. Cardiology Clinics 2000;18: 893-910.
4. Lange A, Mankad P, Walayat M, et al. Transthoracic 3-D echocardiography in the preoperative assessment of atrioventricular defect morphology.Am J Cardiol 2000;85:630-635.
5. Acar P, Roux D, Dulac Y, Rouge P, Aggoun Y. Transthoracic 3-D echocardiography prior to closure of atrial septal defects in children. Cardiol Young 2003;13:58-63.
6. Acar P, Abdel-Massih T, Douste-Blazy M, et al. . Assessment of muscular VSD closure by transcatheter or surgical approach: a 3-D echocardiographic study.Eur J Echocardiogr 2002;3:185-191.
7. Borges AC, Witt C, Bartel T, et al.. Preoperative two-dimensional and three-dimensional echocardiographic assessment of heart tumors. Ann Thorac Surg 1996;61:1163-1167
8. Mahmood F, Karthik S, Subramaniam B, et al. Intraoperative application of geometric three-dimensional mitral valve assessment package: a feasibility study. J Cardiothorac Vasc Anesth2008; 22: 292-29
9. Abraham T, Warner J, Kon N, et al. . Feasibility, accuracy, and incremental value of intraoperative three-dimensional transesophageal echocardiography in valve surgery. Am J Cardiol 1997;80:1577-1582
10. Ahmed S, Nanda N, Miller A, et al.. Usefulness of transesophageal three-dimensional echocardiography in the identification of individual segment/scallop prolapse of the mitral valve. Echocardiography 2003;20:203-9
11. De Castro S, Salandin V, Cartoni D, et al.. Qualitative and quantitative evaluation of mitral valve morphology by intraoperative volume-rendered three-dimensional echocardiography. J Heart Valve Dis 2002; 11: 173-180.
12. George S, Al-Russeh S, Amrani M. Mitral annulus distortion during beating heart surgery: a potential cause for hemodynamic disturbance – a three-dimensional echocardiographic reconstruction study. Ann Thorac Surg 2002;73:1424-1430
13. Shernan S, Shook D, Fox J. Feasibility of real time three-dimensional intraoperative transesophageal echocardiography using a matrix transducer. JACC 2007 49;119A
14. Sugeng L, Shernan S, Salgo I, et al. .Real-Time three-dimensionatransesophageal echocardiography using fully-sampled matrix array probe. J Am Coll Cardiol 2008 ;52;446-9
15. Sugeng L, Shernan S, Weinert L, et al. Real-Time 3D Transesophageal echocardiography in valve disease: comparison with surgical findings and evaluation of prosthetic valves. J Am Soc Echocardiogr 2008;21:1347-54.
16. Jungwirth B, Mackensen B. Real-time 3-dimensional echocardiography in the operating room. Sem Cardiothorac Vasc Anesth 2010;12:248-264
17. Vegas a, Meineri M. Three-dimensional rchocardiography is a major advance for intraoperative clinical management of patients undergoing cardiac surgery: a core review. Anesth Analg 2010;110:1548-73
18. Nomoto K, Hollinger I, DiLuozzo G, Fischer GW. Recognition of a cleft mitral valve utilizing real-time three-dimensional transoesophageal echocardiography. Eur J Echocardiogr. 2009;10:367-9
19. Castillo JG, Anyanwu AC, Adams DH, et al. Real-time 3-dimensional echocardiographic assessment of current continuous-flow rotary left ventricular assist devices. J Cardiothorac Vasc Anesth. 2009;23:702-10
20. Lee MS, Stelzer P, Varghese R, Fischer GW. Assessment of surgical septal myectomy by real-time 3-dimensional transesophageal echocardiography. J Cardiothorac Vasc Anesth. 2010.
21. Fischer GW, Anyanwu AC, Adams DH. Change in surgical management as a consequence of real-time 3D TEE: assessment of left ventricular function. Semin Cardiothorac Vasc Anesth. 2009;13:238-40
22. Mizuguchi KA, Burch TM, Bulwer BE, et al. Thrombus or bilobar left atrial appendage? Diagnosis by real-time three-dimensional transesophageal echocardiography. Anesth Analg. 2009;108:70-2.
23. Azran MS, Kwong R, Chen FY, Shernan SK. A potential use for intraoperative three-dimensional transesophageal echocardiography in predicting left ventricular chamber dimensions and ejection fraction after aneurysm resection. Anesth Analg. 2010;111:1362-5.
24. Fischer GW, Salgo IS, Adams DH. Real-time three-dimensional transesophageal echocardiography: the matrix revolution. J Cardiothorac Vasc Anesth. 2008;22:904-12.
25. Mackensen B, Swaminathan M, Mathew J. Pro: Three-dimensional transesophageal echocardiography is a major advance for intraoperative clinical management of patients undergoing cardiac surgery. Anesth Analg 2010;1574-1578.
26. D'Ambra M. Con: Three-dimensional transesophageal echocardiography is a major advance for intraoperative clinical management of patients undergoing cardiac surgery. Anesth Analg 2010;1579-1580.

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

Update on thoracic epidural anaesthesia: Are the benefits worth the risks and trouble?

Hendrik Freise MD, Hugo K. Van Aken, MD, PhD
Department of Anesthesiology and Intensive Care Medicine
University Hospital Muenster, Albert Schweitzer Strasse 33, 48149 Muenster

RUNNING TITLE: RISKS AND BENEFITS OF THORACIC EPIDURAL ANAESTHESIA

Summary Statement: Thoracic epidural anaesthesia can improve the perioperative morbidity and outcome. The risk of epidural bleeding and infections must be balanced against procedure specific benefits of TEA for optimal perioperative management.

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.

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 to perform TEA. Infectious complications are rare and associated with better prognosis. Close 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 been established as a cornerstone in the perioperative care after thoracic and major abdominal surgery providing most effective analgesia.[1,2] Beyond its analgesic properties, TEA´s effects on the postoperative neurohumoral stress response, cardiovascular pathophysiology and intestinal dysfunction have been in the focus of both clinical and experimental investigations for years.[3-7] However, as an invasive technique TEA is related to 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.

The purpose of this review is to outweigh the perioperative risks related to TEA and analgesic technique and 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

The term stress usually describes a state of increased sympathetic activity that is accompanied by distinct changes in the host's hormonal and immune response as well as the coagulation system.[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 arrhythmias.[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] Raised Corticotropin-Releasing-Hormone-levels reduce cardiac NO-release and increase the endothelin production. This aggravates coronary endothelial dysfunction.[15] Stress can induce a pro-coagulatory state in the absence of any trauma.[16] This effect is prolonged with increasing age.[17] 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.[18,19] 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.[7,22,23] A pro-coagulant state has been repeatedly shown after major abdominal and orthopaedic surgery and persists weeks after surgery.[23-25] As a consequence

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

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.[26]

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.[27] 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.[28,29]

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.[30-32] 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.[30,33,34] 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.[30,35,36]

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.[32,37] A thoracic sympathetic block was preoperatively demonstrated by thermography in TEA induced by low concentration and high volume of local anesthetic.[38] 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.[39] 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.[28] 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.[35] 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.[40]

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 induced renal sympathetic block and increased cardiac sympathetic block via baroreceptor-reflexes. There are no data concerning sensoric block in this model.[32] 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 40. 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.[30] Consequently, the concentration of local anesthetic might not only determine the intensity but also extent of the sympathetic block.[40,41] A higher volume of Bupivacaine 0,25% injected at a midthoracic level induced a sympathetic block including the complete sympathetic innervation of the legs.[38]

ANTI-ISCHEMIC EFFECTS OF TEA IN CARDIAC AND NON-CARDIAC SURGERY

TEA has been repeatedly shown to decrease adverse perioperative cardiac events.[3,42] A superior pain relief with concomitant reduction of the postoperative stress response and systemic sympathetic activity is most likely to contribute to this effect.[1,43,44] 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.[45,46] 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.[47] 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.[48] 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.[49,50] However, a recent meta-analysis showed a decreased rate of combined end-points myocardial infarction and mortality after cardiac surgery in the

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

presence of neuraxial blockade.[49] Furthermore, in non-cardiac high risk surgical patients continuous TEA prevented myocardial infarction.[42]

INTESTINAL PERFUSION

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.[51,52] In acute experimental pancreatitis and in sepsis TEA improved mucosal capillary perfusion.[53,54] In healthy rats a shift from intermittent to continuous capillary perfusion in the face of mild hypotension was recorded during TEA.[55] Similarly, in patients undergoing esophagectomy continuous epidural infusion of Bupivacaine without a bolus dose increased anastomotic mucosal blood flow compared to the control group.[56] 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 altered hemodynamic regulation.[56]

However, a number of clinical and experimental studies revealed adverse effects of TEA on parameters of intestinal perfusion.[57-60] Only recently in 10 patients undergoing esophagectomy TEA has been demonstrated to reduce laser Doppler flow in the distal gastric tube mucosa.[61] 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.[57,58,60,61] Cardiac output remained stable in only one of these studies,[60] but was decreased up to 35% in two other.[57,61] 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.[57,58] The clinical study described a sensoric block reaching Th4.[59] 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.[38]

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.[62] Pain, increased sympathetic tone, the use of systemic opioid analgesia and intestinal neuroinflammatory processes contribute to intestinal hypomotility.[63] The faster resolution of postoperative ileus after major open surgery is widely undisputed and attributed to superior pain therapy, reduced opioid consumption and sympathetic block.[6,64] 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.[65] TEA resulted in a faster resolution of postoperative ileus after major non-intestinal surgery also.[66]

The use of TEA in the setting of fast-track-regimen and minimal invasive approaches for major procedures has been questioned.[6] Two recent studies of TEA after laparoscopic surgery reported improved bowel motility,[67,68] while one other did not prove an effect of TEA.[69] However, differences in study design, technique of TEA and the surgical procedures do hinder comparison and interpretation of the data. The faster resolution of ileus was demonstrated on the background of a non-accelerated standard care. Surgery lasted about 3h and the surgical cases included major resections, such as hemicolectomy, in 12% to 55%.[67,68] In contrast to this, TEA failed to exert beneficial effects when added to an established fast-track-program after laparoscopic sigmoidal resection with a duration of surgery of 2h.[69]

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.[59] 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.[61] 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.[56]

Data on anastomotic patency is also equivocal until today. Both increased rate of insufficiency and improved anastomotic healing has been reported.[70] The latter finding is supported by a recent retrospective analysis of esophageal anastomosis, demonstrating a 70% risk-reduction for anastomotic leak in the TEA group.[71] This protective effect might be of tremendous importance in the light of the five-fold increase in mortality in patients with anastomotic leak.

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.[67-69] Superior pain therapy and ameliorated metabolic response are related to improved quality of life after colonic resection.[72,73] A recent meta-analysis

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

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.[74] However, two recent clinical studies revealed conflicting result with respect to pulmonary complications after esophagectomy and pneumonectomy.[75, 76]

Rodgers and coworker demonstrated a 30% relative risk reduction of fatal outcome after surgery in unselected patients with neuraxial anaesthesia. The evaluation included lumbar and spinal anaesthesia.[3] These findings were corroborated by Wu, who retrospectively demonstrated reduced mortality in the TEA-group after colectomy and lung resections.[77,78] 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.[49] 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.[79,80]

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.[81,82] 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 83. These studies attracted attention to regional anaesthesia as a potential tool to influence long-term outcome by perioperative measures.[84]

Only recently four retrospective studies demonstrated reduced tumor recurrence rate and improved survival after regional anaesthesia in important tumor entities.[85-88] Additional retrospective data from colonic surgery suggest that age might influence the effects of TEA on cancer recurrence.[89] Morphine has been repeatedly shown to reduce Natural Killer cell activity and to promote growth in experimental colonic cancer metastasis and experimental breast cance.[90-93] Hypothermia and adrenergic response also promote experimental tumor growth.[94] Tumor growth can be prevented by effective sympathetic block and analgesia in mice.[95] The observed protective effects of regional anaesthesia might be therefore based both on an opioid-sparing effect and on reduced neurohumoral stress response.

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.[96] 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.[97]

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. Epidural bleeding after epidural anaesthesia has an estimated incidence of 1:2,700 to 1:5,400.[1,98,99] Recently, in a series of 10,000 TEA no epidural haematoma was described.[1] This marked range of risk is related to different practice of perioperative thrombembolism prophylaxis and the implementation of specific guidelines for the use of epidural analgesia and anaesthesia. The incidence of epidural haematoma furthermore differs with the site of insertion and the procedure. While obstetric patients have an extremely low rate of epidural bleeding, perioperative lumbar epidural anaesthesia is more frequently complicated by bloody puncture and epidural haematoma than thoracic epidural catheterization.[1,100] Elderly female scheduled for lower limb arthroplasty have been repeatedly found to carry an especially high risk. In these patients alternative therapeutic strategies needs to be considered.[1]

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.[101] 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.

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

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.[102,103] 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.[100]

Withdrawal of Aspirin. In the western countries approximately 1.8 million coronary stents are implanted each year[104] and 500.000 strokes occur annually in the European union.[105] 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.[106,107] This rebound effect is aggravated by the prothrombotic and proinflammatory state induced by surgery. In case of antiplatelet drug discontinuation within 3 weeks after stenting, mortality is to 30 - 86%.[104] Late stent thrombosis after antiplatelet drug discontinuation can occur more than one year after stenting.[108,109] Consequently it has become consensus to continue antiplatelet medication in almost all 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.[104]

The use of perioperative TEA must not lead to cessation of low dose acetylsalicylic acid prescribed for secondary prophylaxis. There is most probably no increase in the rate of spinal epidural haematoma during low dose ASS intake.[102] However, the combination of ASS with other 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 ASS-prophylaxis.

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.[110] Estimates of incidence vary widely.[110] 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.[100] In pediatric postoperative pain therapy epidural infections and abscesses are also rare.[111] 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.[110,112] 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 100. 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.[100]

CONCLUSIONS

TEA provides optimal pain therapy in a wide range of surgical procedures and might reduce 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.

Funding: This work was supported solely from institutional and/or departmental sources

Conflict of Interest: The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript

REFERENCES

1. Popping DM, Zahn PK, Van Aken HK, Dasch B, Boche R, Pogatzki-Zahn EM. Effectiveness and safety of postoperative pain management: a survey of 18 925 consecutive patients between 1998 and 2006 (2nd revision): a database analysis of prospectively raised data. Br J Anaesth 2008; 101: 832-40
2. Royse C, Royse A, Soeding P, Blake D, Pang J. Prospective randomized trial of high thoracic epidural analgesia for coronary artery bypass surgery. Ann Thorac Surg 2003; 75: 93-100
3. Rodgers A, Walker N, Schug S, et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. BMJ 2000; 321: 1493
4. Liu SS. Anesthesia and analgesia for colon surgery. Reg Anesth Pain Med 2004; 29: 52-7
5. Kozian A, Schilling T, Hachenberg T. Non-analgetic effects of thoracic epidural anaesthesia. Curr Opin Anaesthesiol 2005; 18: 29-34
6. Liu SS, Wu CL. Effect of postoperative analgesia on major postoperative complications: a systematic update of the evidence. Anesth Analg 2007; 104: 689-702
7. Brodner G, Van Aken H, Hertle L, et al. Multimodal perioperative management--combining thoracic epidural analgesia, forced mobilization, and oral nutrition--reduces hormonal and metabolic stress and improves convalescence after major urologic surgery. Anesth Analg 2001; 92: 1594-600
8. Holte K, Kehlet H. Epidural anaesthesia and analgesia - effects on surgical stress responses and implications for postoperative nutrition. Clin Nutr 2002; 21: 199-206

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

9. Sedowofia K, Barclay C, Quaba A, et al. The systemic stress response to thermal injury in children. Clin Endocrinol (Oxf) 1998; 49: 335-41
10. Woolf PD, McDonald JV, Feliciano DV, Kelly MM, Nichols D, Cox C. The catecholamine response to multisystem trauma. Arch Surg 1992; 127: 899-903
11. Leor J, Poole WK, Kloner RA. Sudden cardiac death triggered by an earthquake. N Engl J Med 1996; 334: 413-9
12. Wilbert-Lampen U, Leistner D, Greven S, et al. Cardiovascular events during World Cup soccer. N Engl J Med 2008; 358: 475-83
13. Meissner A, Rolf N, Van Aken H. Thoracic epidural anesthesia and the patient with heart disease: benefits, risks, and controversies. Anesth Analg 1997; 85: 517-28
14. Nabel EG, Ganz P, Gordon JB, Alexander RW, Selwyn AP. Dilation of normal and constriction of atherosclerotic coronary arteries caused by the cold pressor test. Circulation 1988; 77: 43-52
15. Wilbert-Lampen U, Straube F, Trapp A, Deutschmann A, Plasse A, Steinbeck G. Effects of corticotropin-releasing hormone (CRH) on monocyte function, mediated by CRH-receptor subtype R1 and R2: a potential link between mood disorders and endothelial dysfunction? J Cardiovasc Pharmacol 2006; 47: 110-6
16. Wirtz PH, von Kanel R, Emini L, Suter T, Fontana A, Ehlert U. Variations in anticipatory cognitive stress appraisal and differential proinflammatory cytokine expression in response to acute stress. Brain Behav Immun 2007; 21: 851-9
17. Wirtz PH, Redwine LS, Baertschi C, Spillmann M, Ehlert U, von Kanel R. Coagulation activity before and after acute psychosocial stress increases with age. Psychosom Med 2008; 70: 476-81
18. Sambola A, Osende J, Hathcock J, et al. Role of risk factors in the modulation of tissue factor activity and blood thrombogenicity. Circulation 2003; 107: 973-7
19. Gidron Y, Gilutz H, Berger R, Huleihel M. Molecular and cellular interface between behavior and acute coronary syndromes. Cardiovasc Res 2002; 56: 15-21
20. Choyce A, Avidan MS, Harvey A, et al. The cardiovascular response to insertion of the intubating laryngeal mask airway. Anaesthesia 2002; 57: 330-3
21. Pernerstorfer T, Krafft P, Fitzgerald RD, et al. Stress response to tracheal intubation: direct laryngoscopy compared with blind oral intubation. Anaesthesia 1995; 50: 17-22
22. Marana E, Scambia G, Colicci S, et al. Leptin and perioperative neuroendocrine stress response with two different anaesthetic techniques. Acta Anaesthesiol Scand 2008; 52: 541-6
23. Kobayashi M, Tsujitani S, Kurisu Y, Kaibara N. Responses of cytokines and coagulation-fibrinolytic states to surgical stress following esophagectomy. Hepatogastroenterology 2004; 51: 1376-8
24. Dahl OE. Mechanisms of hypercoagulability. Thromb Haemost 1999; 82: 902-6
25. Sweetland S, Green J, Liu B, et al. Duration and magnitude of the postoperative risk of venous thromboembolism in middle aged women: prospective cohort study. BMJ 2009; 339: b4583
26. Bangalore S, Wetterslev J, Pranesh S, Sawhney S, Gluud C, Messerli FH. Perioperative beta blockers in patients having non-cardiac surgery: a meta-analysis. Lancet 2008; 372: 1962-76
27. Clemente A, Carli F. The physiological effects of thoracic epidural anesthesia and analgesia on the cardiovascular, respiratory and gastrointestinal systems. Minerva Anestesiol 2008; 74: 549-63
28. Freise H, Anthonsen S, Fischer LG, Van Aken HK, Sielenkamper AW. Continuous thoracic epidural anesthesia induces segmental sympathetic block in the awake rat. Anesth Analg 2005; 100: 255-62
29. Grassi G, Esler M. How to assess sympathetic activity in humans. J Hypertens 1999; 17: 719-34
30. Magnusdottir H, Kirno K, Ricksten SE, Elam M. High thoracic epidural anesthesia does not inhibit sympathetic nerve activity in the lower extremities. Anesthesiology 1999; 91: 1299-304
31. Hogan QH, Kulier A, Bosnjak ZJ, Kampine JP. Sympathetic and mesenteric venous responses to baroreceptor or chemoreceptor stimulation during epidural anesthesia in rabbits. Anesthesiology 1996; 85: 1413-21
32. Taniguchi M, Kasaba T, Takasaki M. Epidural anesthesia enhances sympathetic nerve activity in the unanesthetized segments in cats. Anesth Analg 1997; 84: 391-7
33. Cook PR, Malmqvist LA, Bengtsson M, Tryggvason B, Lofstrom JB. Vagal and sympathetic activity during spinal analgesia. Acta Anaesthesiol Scand 1990; 34: 271-5
34. Introna R, Yodlowski E, Pruett J, Montano N, Porta A, Crumrine R. Sympathovagal effects of spinal anesthesia assessed by heart rate variability analysis. Anesth Analg 1995; 80: 315-21
35. Adolphs J, Schmitt TK, Schmidt DK, et al. Evaluation of sympathetic blockade after intrathecal and epidural lidocaine in rats by laser Doppler perfusion imaging. Eur Surg Res 2005; 37: 50-9
36. Eisenach JH, Pike TL, Wick DE, et al. A comparison of peripheral skin blood flow and temperature during endoscopic thoracic sympathotomy. Anesth Analg 2005; 100: 269-76
37. Hogan QH, Stekiel TA, Stadnicka A, Bosnjak ZJ, Kampine JP. Region of epidural blockade determines sympathetic and mesenteric capacitance effects in rabbits. Anesthesiology 1995; 83: 604-10
38. Freise H, Meissner A, Lauer S, et al. Thoracic epidural analgesia with low concentration of bupivacaine induces thoracic and lumbar sympathetic block: a randomized, double-blind clinical trial. Anesthesiology 2008; 109: 1107-12
39. Simeoforidou M, Vretzakis G, Bareka M, et al. Thoracic Epidural Analgesia With Levobupivacaine for 6 Postoperative Days Attenuates Sympathetic Activation After Thoracic Surgery. J Cardiothorac Vasc Anesth
40. Hopf HB, Weissbach B, Peters J. High thoracic segmental epidural anesthesia diminishes sympathetic outflow to the legs, despite restriction of sensory blockade to the upper thorax. Anesthesiology 1990; 73: 882-9
41. Ginosar Y, Weiniger CF, Kurz V, Babchenko A, Nitzan M, Davidson E. Sympathectomy-mediated vasodilatation: a randomized concentration ranging study of epidural bupivacaine. Can J Anaesth 2009; 56: 213-21
42. Beattie WS, Badner NH, Choi P. Epidural analgesia reduces postoperative myocardial infarction: a meta-analysis. Anesth Analg 2001; 93: 853-8
43. Holte K, Kehlet H. Effect of postoperative epidural analgesia on surgical outcome. Minerva Anestesiol 2002; 68: 157-61
44. Kehlet H. The endocrine-metabolic response to postoperative pain. Acta Anaesthesiol Scand Suppl 1982; 74: 173-5
45. Olausson K, Magnusdottir H, Lurje L, Wennerblom B, Emanuelsson H, Ricksten SE. Anti-ischemic and anti-anginal effects of thoracic epidural anesthesia versus those of conventional medical therapy in the treatment of severe refractory unstable angina pectoris. Circulation 1997; 96: 2178-82
46. Nygard E, Kofoed KF, Freiberg J, et al. Effects of high thoracic epidural analgesia on myocardial blood flow in patients with ischemic heart disease. Circulation 2005; 111: 2165-70
47. Schmidt C, Hinder F, Van Aken H, et al. The effect of high thoracic epidural anesthesia on systolic and diastolic left ventricular function in patients with coronary artery disease. Anesth Analg 2005; 100: 1561-9
48. Berendes E, Schmidt C, Van Aken H, et al. Reversible cardiac sympathectomy by high thoracic epidural anesthesia improves regional left ventricular function in patients undergoing coronary artery bypass grafting: a randomized trial. Arch Surg 2003; 138: 1283-90; discussion 91
49. Bignami E, Landoni G, Biondi-Zoccai GG, et al. Epidural Analgesia Improves Outcome in Cardiac Surgery: A Meta-analysis of Randomized Controlled Trials. J Cardiothorac Vasc Anesth 2009
50. Liu SS, Block BM, Wu CL. Effects of perioperative central neuraxial analgesia on outcome after coronary artery bypass surgery: a meta-analysis. Anesthesiology 2004; 101: 153-61
51. Ai K, Kotake Y, Satoh T, Serita R, Takeda J, Morisaki H. Epidural anesthesia retards intestinal acidosis and reduces portal vein endotoxin concentrations during progressive hypoxia in rabbits. Anesthesiology 2001; 94: 263-9
52. Kapral S, Gollmann G, Bachmann D, et al. The effects of thoracic epidural anesthesia on intraoperative visceral perfusion and metabolism. Anesth Analg 1999; 88: 402-6
53. Daudel F, Freise H, Westphal M, et al. Continuous Thoracic Epidural Anesthesia Improves Gut Mucosal Microcirculation in Rats with Sepsis. Shock 2007
54. Freise H, Lauer S, Anthonsen S, et al. Thoracic epidural analgesia augments ileal mucosal capillary perfusion and improves survival in severe acute pancreatitis in rats. Anesthesiology 2006; 105: 354-9
55. Sielenkamper AW, Eicker K, Van Aken H. Thoracic epidural anesthesia increases mucosal perfusion in ileum of rats. Anesthesiology 2000; 93: 844-51
56. Michelet P, Roch A, D'Journo XB, et al. Effect of thoracic epidural analgesia on gastric blood flow after oesophagectomy. Acta Anaesthesiol Scand 2007; 51: 587-94
57. Schwarte LA, Picker O, Hohne C, Fournell A, Scheeren TW. Effects of thoracic epidural anaesthesia on microvascular gastric mucosal oxygenation in physiological and compromised circulatory conditions in dogs. Br J Anaesth 2004; 93: 552-9
58. Adolphs J, Schmidt DK, Korsukewitz I, et al. Effects of thoracic epidural anaesthesia on intestinal microvascular perfusion in a rodent model of normotensive endotoxaemia. Intensive Care Med 2004; 30: 2094-101
59. Sala C, Garcia-Granero E, Molina MJ, Garcia JV, Lledo S. Effect of epidural anesthesia on colorectal anastomosis: a tonometric assessment. Dis Colon Rectum 1997; 40: 958-61

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

60. Gould TH, Grace K, Thorne G, Thomas M. Effect of thoracic epidural anaesthesia on colonic blood flow. Br J Anaesth 2002; 89: 446-51

61. Al-Rawi OY, Pennefather SH, Page RD, Dave I, Russell GN. The effect of thoracic epidural bupivacaine and an intravenous adrenaline infusion on gastric tube blood flow during esophagectomy. Anesth Analg 2008; 106: 884-7, table of contents

62. Fruhwald S, Holzer P, Metzler H. Gastrointestinal motility in acute illness. Wien Klin Wochenschr 2008; 120: 6-17

63. Bauer AJ. Mentation on the immunological modulation of gastrointestinal motility. Neurogastroenterol Motil 2008; 20 Suppl 1: 81-90

64. Jorgensen H, Wetterslev J, Moiniche S, Dahl JB. Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. Cochrane Database Syst Rev 2000: CD001893

65. Kuo CP, Jao SW, Chen KM, et al. Comparison of the effects of thoracic epidural analgesia and i.v. infusion with lidocaine on cytokine response, postoperative pain and bowel function in patients undergoing colonic surgery. Br J Anaesth 2006; 97: 640-6

66. Blumenthal S, Min K, Nadig M, Borgeat A. Double epidural catheter with ropivacaine versus intravenous morphine: a comparison for postoperative analgesia after scoliosis correction surgery. Anesthesiology 2005; 102: 175-80

67. Taqi A, Hong X, Mistraletti G, Stein B, Charlebois P, Carli F. Thoracic epidural analgesia facilitates the restoration of bowel function and dietary intake in patients undergoing laparoscopic colon resection using a traditional, nonaccelerated, perioperative care program. Surg Endosc 2007; 21: 247-52

68. Zingg U, Miskovic D, Hamel CT, Erni L, Oertli D, Metzger U. Influence of thoracic epidural analgesia on postoperative pain relief and ileus after laparoscopic colorectal resection : Benefit with epidural analgesia. Surg Endosc 2009; 23: 276-82

69. Turunen P, Carpelan-Holmstrom M, Kairaluoma P, et al. Epidural analgesia diminished pain but did not otherwise improve enhanced recovery after laparoscopic sigmoidectomy: a prospective randomized study. Surg Endosc 2009; 23: 31-7

70. Fotiadis RJ, Badvie S, Weston MD, Allen-Mersh TG. Epidural analgesia in gastrointestinal surgery. Br J Surg 2004; 91: 828-41

71. Michelet P, D'Journo XB, Roch A, et al. Perioperative risk factors for anastomotic leakage after esophagectomy: influence of thoracic epidural analgesia. Chest 2005; 128: 3461-6

72. Carli F, Mayo N, Klubien K, Schricker T, Trudel J, Belliveau P. Epidural analgesia enhances functional exercise capacity and health-related quality of life after colonic surgery: results of a randomized trial. Anesthesiology 2002; 97: 540-9

73. Lattermann R, Carli F, Schricker T. Epidural blockade suppresses lipolysis during major abdominal surgery. Reg Anesth Pain Med 2002; 27: 469-75

74. Popping DM, Elia N, Marret E, Remy C, Tramer MR. Protective effects of epidural analgesia on pulmonary complications after abdominal and thoracic surgery: a meta-analysis. Arch Surg 2008; 143: 990-9; discussion 1000

75. Zingg U, Smithers BM, Gotley DC, et al. Factors Associated with Postoperative Pulmonary Morbidity After Esophagectomy for Cancer. Ann Surg Oncol

76. Powell ES, Cook D, Pearce AC, et al. A prospective, multicentre, observational cohort study of analgesia and outcome after pneumonectomy. Br J Anaesth

77. Wu CL, Rowlingson AJ, Herbert R, Richman JM, Andrews RA, Fleisher LA. Correlation of postoperative epidural analgesia on morbidity and mortality after colectomy in Medicare patients. J Clin Anesth 2006; 18: 594-9

78. Wu CL, Sapirstein A, Herbert R, et al. Effect of postoperative epidural analgesia on morbidity and mortality after lung resection in Medicare patients. J Clin Anesth 2006; 18: 515-20

79. Svircevic V, Nierich AP, Moons KG, et al. Thoracic Epidural Anesthesia for Cardiac Surgery: A Randomized Trial. Anesthesiology; 114: 262-70

80. Caputo M, Alwair H, Rogers CA, et al. Thoracic Epidural Anesthesia Improves Early Outcomes in Patients Undergoing Off-pump Coronary Artery Bypass Surgery: A Prospective, Randomized, Controlled Trial. Anesthesiology; 114: 380-90

81. Liu Z, Jiang M, Zhao J, Ju H. Circulating tumor cells in perioperative esophageal cancer patients: quantitative assay system and potential clinical utility. Clin Cancer Res 2007; 13: 2992-7

82. Lurje G, Schiesser M, Claudius A, Schneider PM. Circulating tumor cells in gastrointestinal malignancies: current techniques and clinical implications. J Oncol 2010; 2010: 392652

83. Vallejo R, Hord ED, Barna SA, Santiago-Palma J, Ahmed S. Perioperative immunosuppression in cancer patients. J Environ Pathol Toxicol Oncol 2003; 22: 139-46

84. Eisenach JC, Borgeat A, Bosnjak ZJ, et al. 2008 in review: advancing medicine in anesthesiology. Anesthesiology 2008; 109: 962-72

85. Christopherson R, James KE, Tableman M, Marshall P, Johnson FE. Long-term survival after colon cancer surgery: a variation associated with choice of anesthesia. Anesth Analg 2008; 107: 325-32

86. Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? Anesthesiology 2006; 105: 660-4

87. Biki B, Mascha E, Moriarty DC, Fitzpatrick JM, Sessler DI, Buggy DJ. Anesthetic technique for radical prostatectomy surgery affects cancer recurrence: a retrospective analysis. Anesthesiology 2008; 109: 180-7

88. Wuethrich PY, Hsu Schmitz SF, Kessler TM, et al. Potential influence of the anesthetic technique used during open radical prostatectomy on prostate cancer-related outcome: a retrospective study. Anesthesiology; 113: 570-6

89. Gottschalk A, Ford JG, Regelin CC, et al. Association between epidural analgesia and cancer recurrence after colorectal cancer surgery. Anesthesiology; 113: 27-34

90. Gupta K, Kshirsagar S, Chang L, et al. Morphine stimulates angiogenesis by activating proangiogenic and survival-promoting signaling and promotes breast tumor growth. Cancer Res 2002; 62: 4491-8

91. Yeager MP, Colacchio TA. Effect of morphine on growth of metastatic colon cancer in vivo. Arch Surg 1991; 126: 454-6

92. Yeager MP, Colacchio TA, Yu CT, et al. Morphine inhibits spontaneous and cytokine-enhanced natural killer cell cytotoxicity in volunteers. Anesthesiology 1995; 83: 500-8

93. Farooqui M, Li Y, Rogers T, et al. COX-2 inhibitor celecoxib prevents chronic morphine-induced promotion of angiogenesis, tumour growth, metastasis and mortality, without compromising analgesia. Br J Cancer 2007; 97: 1523-31

94. Ben-Eliyahu S, Shakhar G, Rosenne E, Levinson Y, Beilin B. Hypothermia in barbiturate-anesthetized rats suppresses natural killer cell activity and compromises resistance to tumor metastasis: a role for adrenergic mechanisms. Anesthesiology 1999; 91: 732-40

95. Bar-Yosef S, Melamed R, Page GG, Shakhar G, Shakhar K, Ben-Eliyahu S. Attenuation of the tumor-promoting effect of surgery by spinal blockade in rats. Anesthesiology 2001; 94: 1066-73

96. Devereaux PJ, Yang H, Yusuf S, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet 2008; 371: 1839-47

97. Schug S. The effect of neuraxial blockade on peri-operative mortality and major morbidity: An updated Meta-Analysis. Anaesthesia and Intensive Care 2005; 33: 675

98. Christie IW, McCabe S. Major complications of epidural analgesia after surgery: results of a six-year survey. Anaesthesia 2007; 62: 335-41

99. Moen V, Dahlgren N, Irestedt L. Severe neurological complications after central neuraxial blockades in Sweden 1990-1999. Anesthesiology 2004; 101: 950-9

100. Cook TM, Counsell D, Wildsmith JA. Major complications of central neuraxial block: report on the Third National Audit Project of the Royal College of Anaesthetists. Br J Anaesth 2009; 102: 179-90

101. Sanderink GJ, Guimart CG, Ozoux ML, Jariwala NU, Shukla UA, Boutouyrie BX. Pharmacokinetics and pharmacodynamics of the prophylactic dose of enoxaparin once daily over 4 days in patients with renal impairment. Thromb Res 2002; 105: 225-31

102. Gogarten W, Vandermeulen E, Van Aken H, Kozek S, Llau JV, Samama CM. Regional anaesthesia and antithrombotic agents: recommendations of the European Society of Anaesthesiology. Eur J Anaesthesiol

103. Levy JH, Key NS, Azran MS. Novel oral anticoagulants: implications in the perioperative setting. Anesthesiology; 113: 726-45

104. Chassot PG, Delabays A, Spahn DR. Perioperative antiplatelet therapy: the case for continuing therapy in patients at risk of myocardial infarction. Br J Anaesth 2007; 99: 316-28

105. The European Registers of Stroke (EROS) Investigators: Incidence of stroke in europe at the beginning of the 21st century. Stroke 2009; 40: 1557-63

106. Beving H, Zhao C, Albage A, Ivert T. Abnormally high platelet activity after discontinuation of acetylsalicylic acid treatment. Blood Coagul Fibrinolysis 1996; 7: 80-4

107. Burger W, Chemnitius JM, Kneissl GD, Rucker G. Low-dose aspirin for secondary cardiovascular prevention - cardiovascular risks after its perioperative withdrawal versus bleeding risks with its continuation - review and meta-analysis. J Intern Med 2005; 257: 399-414

108. McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet 2004; 364: 1519-21

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

109. Ferrari E, Benhamou M, Cerboni P, Marcel B. Coronary syndromes following aspirin withdrawal: a special risk for late stent thrombosis. J Am Coll Cardiol 2005; 45: 456-9

110. Schulz-Stubner S, Pottinger JM, Coffin SA, Herwaldt LA. Nosocomial infections and infection control in regional anesthesia. Acta Anaesthesiol Scand 2008; 52: 1144-57

111. Sethna NF, Clendenin D, Athiraman U, Solodiuk J, Rodriguez DP, Zurakowski D. Incidence of epidural catheter-associated infections after continuous epidural analgesia in children. Anesthesiology; 113: 224-32

112. Horlocker TT, Wedel DJ. Infectious complications of regional anesthesia. Best Pract Res Clin Anaesthesiol 2008; 22: 451-75

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

Management of the Malignant Hyperthermia Patient in Ambulatory Surgery

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

Malignant Hyperthermia (MH) is an inherited muscle disorder characterized by hypermetabolism and triggered by potent volatile anesthetics and the depolarizing muscle relaxant succinylcholine. Clinical signs include hypercarbia, tachycardia, hyperthermia and metabolic acidosis due to abnormal calcium homeostasis resulting in runaway hypermetabolism in the skeletal muscle. Rhabdomyolysis can occur along with disseminated intravascular coagulopathy (DIC) and multi-system organ failure. Early reports of mortality in excess of 70% have been reduced to less than 10% by improved monitoring resulting in early detection and treatment with dantrolene. Management of MH has become well-established and availability of non-triggering anesthetics as well as increased dissemination of information to the anesthetic provider community has decreased the risk as well as the fears of MH-affected individuals. However, the increase in outpatient procedures over the past decade, with procedures often performed in ambulatory care settings where emergency equipment and access to immediate laboratory support may be limited, have increased concern about treatment of unexpected MH crises.

HISTORY

One of the earliest references to an MH-like problem was 1929 when the French pathologist Ombredanne[1] reported postoperative pallor and hyperthermia associated with high mortality in children, however this condition was not identified as a genetic trait. In 1960 Australian physicians Denborough and Lovell[2] reported the first case of a familial history of anesthetic deaths during ether administration. The reported patient barely survived a halothane-induced MH episode. In 1969 Canadian physicians Kalow and Britt[3] described a metabolic error of muscle metabolism noted in patients recovered from MH episodes, forming the basis for diagnostic contracture testing. In 1975 Harrison,[4] a South African, described the efficacy of dantrolene in treating porcine MH. This became the foundation for successfully managing a condition that had been termed "the anesthesiologist's nightmare" due to its unexpected nature and high mortality.

INCIDENCE

The incidence of MH is reported to range from 1:4500 to 1:60,000 general anesthetics (geographic variation is related to the gene prevalence). Approximately 50% of MH-susceptible individuals have had a previous triggering anesthetic without developing MH.[5] MH is rare in infants and the incidence decreases after 50 years of age with males more commonly reported than females.[6] The reasons for these variations are not understood.

MH has been clearly associated with Central Core Disease, multiminicore disease, and King or King-Denborough Syndrome. Association with other disorders such as Duchenne Muscular Dystrophy, myotonia, mitochondrial myopathies, sudden infant death syndrome (SIDS), and neuroleptic malignant syndrome (NMS) is controversial. Exercise-induced MH-related death in adults, especially during exposure to hot environments, has been reported.[7,8]

MECHANISM

Exposure to triggering anesthetics (all potent volatile anesthetics and succinylcholine) causes decreased control of intracellular calcium resulting in a release of free unbound ionized Ca++ from storage sites in the skeletal muscle. The calcium pumps attempt to restore homeostasis which results in ATP utilization, increased aerobic and anaerobic metabolism, and a runaway metabolic state. Rigidity occurs when unbound myofibrillar Ca++ approaches the contractile threshold.

CLINICAL PRESENTATION

Onset of clinical signs can be acute and fulminant or delayed. MH can occur at any time during the anesthetic, and has been reported to occur as late as 24 hours postoperatively. Trismus or masseter muscle spasm following inhalation induction and succinylcholine is associated with an approximately 50% incidence of MH diagnosed by contracture testing. Trismus is often not associated with signs of a fulminant MH episode, however patients must be closely observed for evidence of hypermetabolism as well as rhabdomyolysis. The presence of whole body rigidity or signs of hypermetabolism following trismus increase the risk of MH susceptibility as an etiology. Elevation of CK postoperatively to greater than 20,000 has a strong association with a subsequent MH diagnosis.

Clinical signs and symptoms reflect a state of increasing hypermetabolism. The onset of hyperthermia can be delayed. The earliest signs of MH include tachypnea (in the nonparalyzed patient) and increased end-tidal CO_2 levels. Rigidity, masseter or whole body, occurs in about 75% of cases. Signs of increased sympathetic activity include tachycardia, dysrhythmias, sweating and hypertension.

Supportive laboratory tests for confirmation of MH diagnosis include elevated end-tidal CO_2, blood gas analysis showing a mixed respiratory-metabolic acidosis, elevated serum creatine phosphokinase (CK)

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

postoperatively, elevated serum and urine myoglobin and increased serum K+, Ca++, and lactate (these findings can be very transient).

TREATMENT

Discontinue triggers immediately and hyperventilate with 100% oxygen. IV Dantrolene should be given early and rapidly when MH is suspected. The initial dosage is 2 mg/kg IV, repeated every five minutes to effect or to a maximum of 10 mg/kg (this limit may be exceeded if necessary). After successful treatment, dantrolene is continued at 1 mg/kg IV q 6 hr for 24 to 48 hours to prevent recrudescence of symptoms. Calcium channel blockers should not be given in the presence of dantrolene as myocardial depression has been demonstrated in swine. Symptomatic treatment during an MH episode may include cooling (stop cooling interventions at 38-39 degrees C to avoid post-treatment hypothermia), antiarrhythmics, management of hyperkalemia, mannitol and/or furosemide to induce diuresis (note that mannitol is present in dantrolene) and sodium bicarbonate. Interventions should be guided by blood gas analysis and clinical signs; administration of dantrolene will usually reverse symptoms rapidly. It is critical that all sites where general anesthesia is administered, including ambulatory and oral surgery centers, have adequate dantrolene supplies to treat an adult patient with MH. Several tragic injuries and deaths have occurred due to delay in treatment in these settings.[9]

Table 1 – Conditions that Mimic MH

Fever (without rigidity)	Fever and/or muscle symptoms	Increased End-Tidal CO_2
Thyrotoxicosis	NMS (psych meds)	Faulty equipment
Sepsis	Hypoxic encephalopathy	Tourniquet (children)
Pheochromocytoma	CSF ionic contract agents	Laparoscopic insufflation
Iatrogenic overheating	Cocaine, amphetamine, ecstasy	
Anticholinergic syndrome	Dystrophinopathy	
	Myotonic syndromes	
	Rhabdomyolysis	

ANESTHESIA FOR MH SUSCEPTIBLE (MHS) PATIENTS

Pretreatment with Dantrolene 1.5-2 mg/kg IV prior to induction is no longer recommended. Choose non-triggering anesthetic agents. Safe anesthetic agents include nitrous oxide, etomidate, ketamine, propofol, all narcotics, all local anesthetics, all barbiturates, all benzodiazepines and all non-depolarizing muscle relaxants. Agents used for reversal of muscle relaxants are also safe. Prepare the machine by removing vaporizers (if possible) or taping over the dials and replacing rubber hoses and soda lime. Flush with high flow oxygen (5 L/m) for 10 minutes.

Standard monitors are used with an emphasis on end-tidal CO_2, oxygen saturation, and core temperature (skin monitors may not reflect core changes). Arterial and central venous pressures need be monitored only if indicated by the surgical procedure or the patient's medical condition. Avoidance of perioperative exposures to potential trace-gas contamination (e.g. the recovery room) is not necessary.

AMBULATORY SETTINGS – SPECIAL CONCERNS FOR MANAGING (MHS) PATIENTS

While the overall incidence of MH episodes is low, the increase in the number of anesthetics in ambulatory care settings over the past decade has resulted in some MH-related deaths in patients with undiagnosed MHS.

Such settings must be prepared to identify and treat acute MH events. Several concerns have been identified in the ambulatory setting:

1. Lack of laboratory backup – identifying MH involves evaluation of acid-base status, serum CK and myoglobin levels and other tests. Ambulatory centers usually do not have immediate access to a laboratory for diagnostic testing.
2. Treatment delay – it is advisable to have dantrolene immediately available in all settings where general anesthetics are delivered, however mixing and administering this medication requires additional medical personnel who may not be available in the ambulatory setting.
3. Transfer from the ambulatory center – patients undergoing an MH episode may be hemodynamically unstable, and transport personnel may not be comfortable with continuing dantrolene treatment. Evaluation at a tertiary care center may further delay treatment and result in worsening symptoms.
4. Ambulatory patients and their families may be "lost to followup" and not receive appropriate genetic counseling after an MH episode.

EVALUATION OF SUSCEPTIBILITY

Patients are referred for evaluation for a number of reasons including unexplained intraoperative death in family members, history of adverse anesthetic event (e.g. trismus), perioperative fever, persistently elevated serum creatine phosphokinase (CK) levels, history of rhabdomyolysis, and associated myopathies (e.g. central core disease). A resting level serum CK level is often obtained in patients suspected of being MHS and may be elevated in approximately 70% of affected individuals.

A clinical grading scale has been devised, and while imperfect, it can help determine whether an individual case fits the diagnosis of MH.

The muscle biopsy contracture testing known as either the *caffeine/halothane contracture test* (CHCT) or the *in vitro contracture test* (IVCT) has always been considered the "gold standard" diagnostic test for MH. Freshly excised muscle, usually from the vastus lateralis or gracilis, is dissected into strips which are mounted in baths and tested with caffeine and halothane alone or in combination; contracture responses are measured

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

Table 2. Criteria Used in the Clinical Grading Scale for Malignant Hyperthermia (MH)

Process	Clinical Criteria	Points
Muscle rigidity	Generalized rigidity Masseter muscle rigidity	15 15
Muscle breakdown	Creatine kinase > 10,000 units/l Cola-colored urine Excess myoglobin in urine or serum K+ > 6 mEq/l	15 5 3
Respiratory acidosis	End-tidal CO_2 > 55 mmHg; $PaCO_2$ > 60 mmHg Inappropriate tachypnea	15 10
Temperature increase	Rapidly increasing temperature Inappropriate temperature > 38.8°C	15 10
Cardiac involvement	Unexplained sinus tachycardia, ventricular tachycardiac, or ventricular fibrillation	3
Family history	MH history in first-degree relative MH history in family, not first-degree relative	15 5

Only the highest score in any one process should be used when more than one event or sign occurs in a process. The more criteria that a patient fulfills, the more likely that an MH episode has occurred. If only one criterion is fulfilled, then malignant hyperthermia is not likely, whereas malignant hyperthermia is almost certain if all criterial are fulfilled. Other criteria to consider include base excess > -8 mEq/L (10 points), pH < 7.25 (10 points), and rapid reversal of malignant hyperthermia signs with dantrolene therapy (5 points). The likelihood according to point score: 0, almost never; 3-9, unlikely; 10-19, somewhat less than likely; 20-34, somewhat greater than likely; 35-49, very likely; ≥ 50, almost certain. Adapted from Larach et al,[10,11] with permission.

and interpreted according to standardized values. Testing centers in North America have been reduced to five due to several factors including reluctance of insurance companies to pay for the expense of surgery and testing and increased availability of genetic testing. Contracture testing cannot be done on children under 5 years or under 20 Kg weight.

MOLECULAR GENETICS

MH is an autosomal dominant trait; therefore, patients with this condition will have inherited it from at least one parent. However, it is quite common for neither parent to have shown signs of MH either because they have not been exposed to triggering anesthesia or because they did not react.

Two MHS-causative genes have been identified: **RYR1** (MHS1 locus) and **CACNA1S** (MHS5 locus).[12] **RYR1** encodes the type 1 ryanodine receptor of skeletal muscle and mutations of this gene are identified in up to 70-80% of individuals with confirmed MH and in patients with Central Core Disease (CCD). More than 180 mutations in **RYR1** have been associated with MH or CCD, with over half appearing in only one or a few families. **CACNA1S** encodes the α1-subunit of the skeletal muscle dihydropyridine receptor L-type calcium channel. Mutations in this gene account for about 1% of all MHS (2 gene mutations identified). Three additional loci have been mapped, but the genes have not been identified: MHS2, MHS4 and MHS6.

Patients must be carefully selected for genetic testing in order to maximize sensitivity. Usually this means either a positive muscle contracture test or strongly suggestive family or clinical histories for MH. In these cases, complete sequence analysis of the entire **RYR1** coding region increases the detection rate to 70-80%. Linkage analysis for all MHS loci is considered in families with multi-generational (at least two) unequivocal MH diagnosis in 10 family members or more. Discordance between contracture testing and molecular genetic testing is observed in up to 10% of individuals.

MHAUS

The Malignant Hyperthermia Association of the United States (MHAUS) is an active organization which provides support for patients and physicians. Their website found at www.MHAUS.org provides resources for patients, families, and medical providers. MHAUS also sponsors a 24-hour hotline for providing assistance to physicians who are managing MH susceptible patients or treating acute MH episodes.

MH HOTLINE

USA and Canada
1 (800) 644-9737 • 1-800-MH HYPER

Outside the US • 0011 315 464 7079

Also associated with MHAUS is the North American MH Registry, situated in Pittsburgh, PA. Information about MH episodes (via the American Medical Record Association AMRA report) and testing is stored in the Registry where it is available for approved research and reporting.

REFERENCES

1. 1. Ombrédanne L. De l'influence de l'anesthésique employé dans la ganése des accidents postopératoires de pâleurhyperthermie observés chez les nourrissons. Rev Med Française 1929;10:617.
2. 2. Denborough M, Lovell R. Anaesthetic Deaths In A Family. Lancet 1960;2:45.
3. 3. Kalow W, Britt B, Terreau M, Haist C. Metabolic Error of Muscle Metabolism After Recovery From Malignant Hyperthermia. Lancet 1970;296:895-8.
4. 4. Harrison GG. Control of the malignant hyperpyrexic syndrome in MHS swine by dantrolene sodium. Br J Anaesth 1975;47:62-5.
5. 5. Bendixen D, Skovgaard LT, Ording H. Analysis of anaesthesia in patients suspected to be susceptible to malignant hyperthermia before diagnostic in vitro contracture test. Acta Anaesthesiol Scand 1997;41:480-4.
6. 6. Larach MG, Gronert GA, Allen GC, Brandom BW, Lehman EB. Clinical presentation, treatment, and complications of malignant hyperthermia in North America from 1987 to 2006. Anesth Analg 2010;110:498-507.
7. 7. Sambuughin N, Capacchione J, Blokhin A, Bayarsaikhan M, Bina S, Muldoon S. The ryanodine receptor type 1 gene variants in African American men with exertional rhabdomyolysis and malignant hyperthermia susceptibility. Clin Genet 2009;76:564-8.
8. 8. Tobin JR, Jason DR, Challa VR, Nelson TE, Sambuughin N. Malignant hyperthermia and apparent heat stroke. Jama 2001;286:168-9.
9. 9. Brandom BW. Ambulatory surgery and malignant hyperthermia. Curr Opin Anaesthesiol 2009;22:744-7.
10. 10. Pollock N, Langton E, MacDonnell N, et al. Malignant hyperthermia and day stay surgery. Anaesth Intensive Care 2006;35:40-45
11. 11. Larach MG, Localio AR, Allen GC, Denborough MA, Ellis FR, Gronert GA, Kaplan RF, Muldoon SM, Nelson TE, Ording H, et al. A clinical grading scale to predict malignant hyperthermia susceptibility. Anesthesiology 1994;80:771-9.
12. 12. Tautz TJ, Urwyler A, Antognini JF, Riou B. Case scenario: Increased end-tidal carbon dioxide: a diagnostic dilemma. Anesthesiology 2010;112:440-6.
13. 13. Rosenberg HS, N.; Dirksen, R. Malignant Hyperthermia Susceptibility. GeneReviews 2010.
14. 14. Brandom BW, Larach MG, Chen MA, Young MC. Complications associated with the administration of dantrolene 1987 to 2006: A report from the North American Malignant Hyperthermia Registry of the MHAUS. Anesth Analg 2011; in press

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

Central Venous Access Guideline Development and Recommendations

Stephen M. Rupp, MD
ASA Task Force Chair, Staff Anesthesiologist, Medical Director Perioperative Services
Virginia Mason Medical Center, Seattle, WA

Placement of central venous catheters (CVC) has major risks for patients. These include: 1) catheter-related blood stream infection leading to sepsis[1,2] and 2) major vascular injury from unintentional entry of a large-bore dilator or catheter into the arterial system.[3-5] In 2009, The American Society of Anesthesiologists Committee on Standards and Practice Parameters chartered a task force to develop a guideline for the membership with the specific goal of helping to reduce or eliminate these complications. Specifically, the purposes of the Guidelines are (1) to provide guidance regarding placement and management of central venous catheters, (2) reduce infectious, mechanical, thrombotic, and other adverse outcomes associated with central venous catheterization, and (3) to improve management of arterial trauma or injury arising from central venous catheterization. This Review Course Lecture will focus on the scientific evidence, opinion surveys and development of resultant recommendations by the task force.

WHAT ARE THE MAJOR COMPLICATIONS FROM CENTRAL VENOUS ACCESS AND WHY ARE THEY IMPORTANT?

Catheter-Related Blood Stream Infections (CRBSI): In 2002, the CDC estimated that there were 80,000 CRBSIs per year in intensive care units (ICU) in the United States and up to 250,000 episodes per year if entire hospitals were assessed rather than just ICUs.1 The associated mortality increase from a CRBSI was estimated to be up to 35%, resulting in approximately 30,000 deaths per year.[1,2] The CDC estimated the cost of caring for CRBSI in the U.S. to range annually from $296M to $2.3B.[1] Fortunately, significant reductions in CRBSI can be obtained by rigorously following specific practices or "bundles" of care[6] (see below). In a recent publication, the CDC estimated that due to these efforts CRBSI in ICU's in the United States had been reduced by 58% by 2009.[7] Still, much work needs to occur. For example, the CDC estimates that in 2009 23,000 CRBSI's still occur per year on inpatient wards and 37,000 occur among patients receiving outpatient dialysis.[7]

Major vascular injury as a result of large-bore dilator or catheter placement in the arterial system: It is estimated that more than 5 million CVCs are placed in the U.S per year.[8] Devastating complications can and do occur when a large-bore dilator or catheter enters the arterial system (typically the carotid artery).[3-5] Stroke, massive hemorrhage, airway compromise and death can occur if this complication is not appropriately managed. Studies show that this complication occurs in approximately 0.1 – 1% of attempts at central venous catheterization.[5, 9-11] While the incidence in highly experienced hands is probably lower, it appears that up to 5,000 of these serious adverse events occurs annually in the United States. If this complication is not managed appropriately nearly 50% of patients will have a major neurologic deficit or die.[5]

While a large-bore dilator or catheter may present the largest risk to the arterial system, a stroke can occur even after a single arterial puncture with a searching needle.[10]

ASA METHODOLOGY ON GUIDELINE DEVELOPMENT

The American Society of Anesthesiologists (ASA) appointed a Task Force of 11 members, including anesthesiologists in both private and academic practice from various geographic areas of the United States and two consulting methodologists from the ASA Committee on Standards and Practice Parameters. The task force used the standard robust ASA methodology of surveying and evaluating primary-source evidence, sampling ASA member and expert opinion to develop evidence-based linkages to specific recommendations. The details of the process are available within the draft guideline which is posted on the ASA website at http://www.asahq.org/For-Members/Clinical-Information/Central-Venous-Access-Guidelines.aspx. Importantly, scientific literature was divided into four categories:

Category A: Supportive Literature. Randomized controlled trials report statistically significant ($p < 0.01$) differences between clinical interventions for a specified clinical outcome.

Level 1: The literature contains multiple randomized controlled trials, and aggregated findings are supported by meta-analysis.[1]*

Level 2: The literature contains multiple randomized controlled trials, but the number of studies is insufficient to conduct a viable meta-analysis for the purpose of these Guidelines.

Level 3: The literature contains a single randomized controlled trial.

Category B: Suggestive Literature. Information from observational studies permits inference of beneficial or harmful relationships among clinical interventions and clinical outcomes.

Level 1: The literature contains observational comparisons (*e.g.*, cohort, case-control research designs) of clinical interventions or conditions and indicates statistically significant differences between clinical interventions for a specified clinical outcome.

Level 2: The literature contains non-comparative observational studies with associative (*e.g.*, relative risk, correlation) or descriptive statistics.

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

Table 1. Interventions to Prevent Infections

	category evidence[1]	ASA members[2]	Consultants[2]	Task Force Recommedation
prophylactic antibiotic routine	D	not routine	not routine	not routine
prophylactic antibiotic immunosuppressed	A2	case-by-case	case-by-case	case-by-case
maximal barrier precautions in "bundle"	B2			recommended
agree to specific aseptic prep steps				
hand washing	D	96%	100%	recommended
sterile full-body drape	D	74%	87%	recommended
sterile gown	D	88%	100%	recommended
sterile gloves	D	100%	100%	recommended
Caps and masks	D	95%	100%	recommended
chlorhexidine vs. iodine skin prep	D			
chlorhexidine w alcohol vs. iodine skin prep	D	strongly agree	strongly agree	recommended
catheters containing antimicrobial agents	A1	in selected pts	in selected pts	in selected patients
selection of catheter insertion site adults				
femoral site higher colonization rate	A3	avoid femoral	avoid femoral	use upper body site
internal jugular vs. subclavian	C3	IJ site preferred	SC site preferred	base on clinical need
catheter fixation technique: suture, staple, tape	D	suture preferred	suture preferred	institutional choice
catheter insertion site dressings				
transparent bio-occulusive	D	strongly agree	strongly agree	recommended
chlorhexidine sponge dressings aults and children	C2	may be used	may be used	may be used
chlorhexidine sponge dressings neonates	D		eqivocal	clinical judgement/protocol
catheter maintenance				
longer catheterizations have higher rates inf	B2	use based on need	use based on need	use based on clinical need
assess need daily	D	strongly agree	strongly agree	recommended
conducting catheter site inspections daily		strongly agree	strongly agree	recommended
periodic changing of catheters	C2			only if signs of infection
change using a new site vs. guidewire	C1	strongly agree	strongly agree	new site preferable
remove promptly when no longer needed		strongly agree	strongly agree	recommended
Prep for accessing an existing central line				
wiping port w antiseptic prior to access	D	strongly agree	strongly agree	wipe before each access
use needleless access sites or ports	A2	agree	agree	use on a case-by-case basis
cap stopcocks or access ports when not in use	D	strongly agree	strongly agree	cap when not in use

1. Category A Evidence = Supportive
Category B Evidence = Suggestive
Category C Evidence = Equivocal
Category D Evidence = Insufficient

2. Survey data are on a 5 point scale:
strongly agree - agree - equivocal - disagree - strongly disagree
result represents the median value of survey

Level 3: The literature contains case reports.

Category C: Equivocal Literature. The literature cannot determine whether there are beneficial or harmful relationships among clinical interventions and clinical outcomes.

Level 1: Meta-analysis did not find significant differences ($p > 0.01$) among groups or conditions.

Level 2: The number of studies is insufficient to conduct meta-analysis, and (1) randomized controlled trials have not found significant differences among groups or conditions or (2) randomized controlled trials report inconsistent findings.

Level 3: Observational studies report inconsistent findings or do *not* permit inference of beneficial or harmful relationships.

Category D: Insufficient Evidence from Literature. The lack of scientific evidence in the literature is described by the following terms.

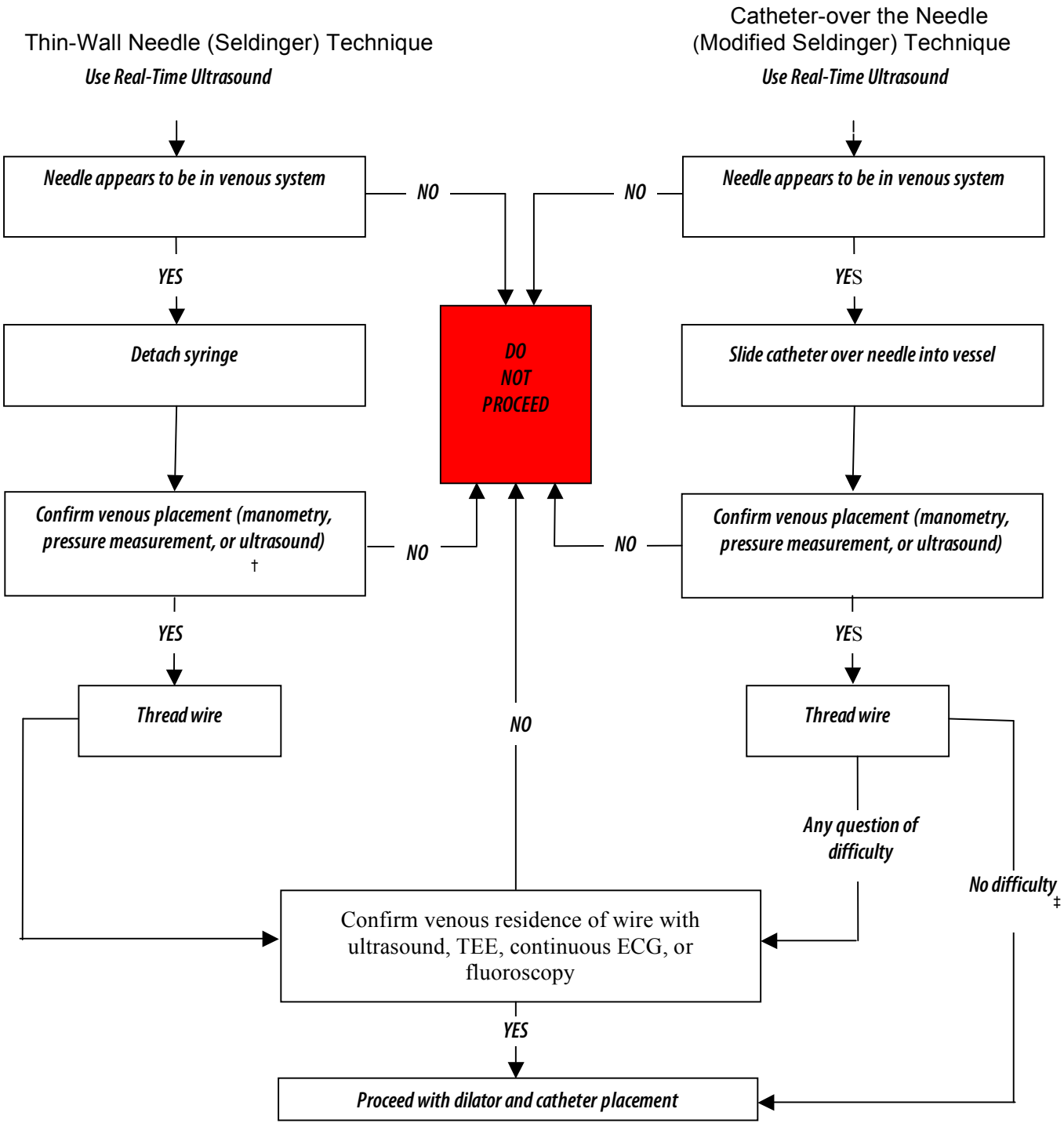
Inadequate: The available literature cannot be used to assess relationships among clinical interventions and clinical outcomes.

Silent: No identified studies address the specified relationships among interventions and outcomes.

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

AMERICAN SOCIETY OF ANESTHESIOLOGISTS

Figure 1: Algorithm for Central Venous Insertion and Verification*



* This algorithm compares the thin-wall needle (i.e., Seldinger) technique vs. the catheter-over-the needle (i.e., Modified-Seldinger) technique in critical safety steps to prevent unintentional arterial placement of a dilator or large-bore catheter. The variation between the two techniques reflects mitigation steps for the risk that the thin-wall needle in the Seldinger technique could move out of the vein and into the wall of an artery between the manometry step and the threading of the wire step.

† For neonates, infants, and children, confirmation of venous placement may take place after the wire is threaded.

‡ Consider confirming venous residence of the wire

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

THE CAUSES OF CATHETER-RELATED BLOOD STREAM INFECTIONS

Most CRBSIs are related to short-term noncuffed, percutaneously placed central venous catheters.[12] Potential sources of catheter infection include 4 key sources: 1) extraluminal (from contiguous skin flora), 2) intraluminal by contamination of the catheter hub and lumen 3) contamination of infusate or extrinsic medication and 4) hematogenously from distant infection.[12] The most frequent cause is extraluminally acquired from cutaneous flora.[12] Hence, strategies to suppress cutaneous colonization and migration have been a focus of preventive efforts. Additionally, most infectious disease experts agree that due to the nature of implanted devices and the body's defense mechanisms all CVC's will eventually become infected over time. Thus, they recommend removing unnecessary catheters when they are no longer needed.

PREVENTING INFECTIOUS COMPLICATIONS

The task force addressed *Resource Preparation* including: (1) assessing the physical environment where central venous catheterization is planned to determine the feasibility of using aseptic techniques, (2) availability of a standardized equipment set, (3) use of an assistant for central venous catheterization, and (4) use of a checklist or protocol for central venous catheter placement and maintenance. The literature was insufficient to specifically evaluate any of these preparations individually. However, several observational studies reported reduced CRBSI rates when ICU-wide protocols or checklists are implemented.[6, 13-16] (Category B2 evidence) For example, Pronovost et al.[6] demonstrated that a rigorous application of a "bundle" of procedures along with a comprehensive unit-based safety program[17] resulted in a large and sustained reduction (up to 66%) in CRBSI. The procedural "bundle" included hand hygiene prior to CVC placement, chlorhexidine skin prep, full-barrier precautions during insertion, avoiding the femoral site if possible, and removing unnecessary catheters. The studies do not permit the assessment of the impact of any single component of a bundled protocol on outcome. With these studies and strong agreement from expert consultants, the task force guideline created recommendations and several practical tools that can be used to deliver the recommended bundles of care. Examples include a sample checklist, a standardized equipment cart, and the duties of an assistant.

The task force evaluated eight other specific interventions intended to prevent infectious complications including: (1) intravenous antibiotic prophylaxis, (2) aseptic techniques (*i.e.*, practitioner aseptic preparation and patient skin preparation), (3) selection of coated or impregnated catheters, (4) selection of catheter insertion site, (5) catheter fixation method, (6) insertion site dressings, (7) catheter maintenance procedures, and (8) aseptic techniques using an existing central venous catheter for injection or aspiration. Table 1 summarizes the scientific evaluation, survey data and task force recommendations on these interventions.

PREVENTION OF MECHANICAL TRAUMA OR INJURY

As mentioned earlier, the prevention of trauma to the arterial system (particularly the carotid artery) was a focus of the task force. Interventions intended to prevent mechanical trauma or injury associated with central venous access that were assessed by the task force included: (1) selection of catheter insertion site, (2) positioning the patient for needle insertion and catheter placement, (3) needle insertion and catheter placement, and (4) monitoring for needle, guide wire, and catheter placement. Table 2 summarizes the scientific evaluation, survey data and task force recommendations on these interventions.

The most important strategy is avoidance of entering the arterial system. Unfortunately, due to anatomic variation, the carotid artery (or a portion thereof) frequently lies under the internal jugular vein. As a needle is advanced, the compressible nature of the internal jugular vein can result in both the anterior and posterior walls of the vessel being punctured simultaneously. In this situation the needle ends up being deep to the vein. These factors (and others) can combine to cause carotid artery puncture during "blind" or "landmark" techniques. The best way to avoid entering the carotid artery during internal jugular venous catheterization is to use *real-time* ultrasound. Meta-analysis of randomized controlled trials indicates that, compared to the landmark approach, *real-time* ultrasound guided venipuncture of the internal jugular vein has the highest first-insertion attempt success rate, reduced access time, higher overall successful cannulation rate and lower rates of arterial puncture.[18-28] This is the strongest evidence in the guideline (category A1 evidence) and is the basis for the recommendation that for elective internal jugular cannulation *real-time* ultrasound guidance be used. This recommendation will bring ASA practice recommendations in line with other agencies and specialties that have adopted this safety strategy.[29-30]

Once the needle is in the internal jugular vein, it is important to ensure that the needle (or catheter) stays in the vein while the wire is threaded and that the wire enters and stays in the vein. Accordingly, sequential safety checks such as manometry[11] or pressure measurement and venous confirmation of the wire (after threading)[31] are important in ensuring that all is well. These added safety checks are needed as it appears that neither ultrasound nor manometry when used alone can eliminate the chance of arterial puncture.[32] The task force designed an algorithm that provides a step-by-step approach, using evidence-based recommendations to reduce and strictly limit the chance of arterial injury by using techniques such as pressure measurement, manometry, and both surface and transesophageal ultrasound[33] (see Figure 1). The algorithm is designed for maximum flexibility according to the anesthesiologist's chosen or favored technique (*e.g.*, thin-walled needle vs. catheter-over-the-needle), and the clinical situation. It includes redundant safety steps that—when used in sequence-

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

Table 2. Interventions to Prevent Mechanical Injury (Adults)

	category evidence[1]	ASA members[2]	Consultants[2]	Task Force Recommedation
selection of insertion site				
thrombotic complications higher w femoral	A3	prefer IJ	prefer IJ	select upper body site
IJ vs. Subclavian for successful venapuncture	C2	prefer IJ	prefer IJ	
IJ vs. Subclavian for complications	C3	prefer IJ	prefer IJ	select based on clinical need
Positioning the patient				
trendelenburg increase IJ diameter if > 6 yo	B2	strongly agree	strongly agree	when feasible use Trendelenburg
Needle insertion, wire and catheter placement				
selection of catheter type		strongly agree	strongly agree	size and type choice based on need
large-bore catherters in carotid cause harm	B3			the smallest size appropriate is best
thin-walled needle vs. catheter-over-needle	D	choice	choice	choice based on skill/experience
limit number of insertion attempts	D	clinical judgment	clinical judgment	clinical judgment
two catheters in one vein causes dysrhythmias	B2	case-by-case	case-by-case	case-by-case
guidance of needle				
use ultrasound for pre-procedural vessel localization		agree	agree	use in elective situations
internal jugular: higher first insertion success	A2			
subclavian vein access	C2			may be used
use ultrasound for guiding needle (real-time)		equivocal	agree	use when IJ is chosen
internal jugular: better 1st pass success, less arterial	A1			
puncture, reduced access time, higher overall success	A1			
verification of needle in vein using one of the below		confirm prior to wire	confirm prior	confirm prior to wire
ultrasound		may		may be used
manometry	B2			use in catheter-over-the needle technique
pressure waveform analysis	D			may be used
venous blood gas	D			silent
absence of pulsatility, blood color	D			do not use
verification of wire in the vein using one of below:		equivocal	agree	use in thin-walled needle technique3
ultrasound	B2			may be used
fluoroscopy	D			may be used
continuous electrocardiography	D			may be used
transesophageal ultrasound	B3			may be used
verification of the catheter in the venous system		agree	strongly agree	confirm with manometry or pressure
fluoroscopy		agree	agree	confirm as soon as clinically appropriate
chest xray	B2			may be used
continuous electrocardiography	B2	agree	agree	may be used
	A2			may be used

1. Category A Evidence = Supportive
Category B Evidence = Suggestive
Category C Evidence = Equivocal
Category D Evidence = Insufficient

2. Survey data are on a 5 point scale:
strongly agree - agree - equivocal - disagree - strongly disagree
result represents the median value of survey
3. and if difficulty encountered in catheter-over-needle technique

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

--virtually eliminates the chance of this devastating complication.

RECOMMENDATIONS FOR MANAGEMENT OF ARTERIAL TRAUMA OR INJURY ARISING FROM CENTRAL VENOUS CATHETERIZATION

Case reports of adult patients with arterial puncture by a large bore catheter/vessel dilator during attempted central venous catheterization report severe complications (*e.g.*, cerebral infarction, arteriovenous fistula, hematoma with airway compromise) following immediate catheter removal; no such complications were reported for adult patients whose catheters were left in place before surgical consultation and repair.[5,34] *(Category B3 evidence)* The guideline recommends that in adults the large-bore dilator or catheter be left in place and that a general surgeon, vascular surgeon or interventional radiologist be immediately consulted regarding surgical or non-surgical catheter removal for adults. Finally, there may be delayed neurologic sequlae from an unintentional arterial injury with a large bore dilator or catheter.[12] Accordingly, the task force recommended that after the injury has been evaluated and a treatment plan has been executed, the anesthesiologist and surgeon should confer regarding relative risks and benefits of proceeding with elective surgery versus deferring surgery to allow for a period of patient observation.

REFERENCES

* All meta-analyses are conducted by the ASA methodology group. Meta-analyses from other sources are reviewed but not included as evidence.

1. O'Grady NP, Alexander M, Dellinger EP et al. Guidelines for the prevention of intravascular catheter-related infections. MMWR Recomm Rep 2002;51(RR-10):1-29
2. Klevens RM, Edwards JR, Richards CL, et al. Public Health Rep 2007;122:160-166
3. Domino KB, Bowdle AT, Posner KL, et al. Injuries and liability related to central venous catheters. A closed claims analysis. Anesthesiology 2004;100:1411-1418
4. Pikwer A, Acosta S, Kolbel T, et al. Management of inadvertent arterial catheterization associated with central venous access procedures. Eur J Endovasc Surg 2009;38:707-714
5. Guilbert MC, Elkouri S, Bracco D, et al. Arterial trauma during central venous catheter insertion: case series, review and proposed algorithm. J Vasc Surg 2008;48:918-925
6. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. NEJM 2006;355:2725-2732
7. Srinivasan A, Wise M, Bell M, et al. Vital signs: Central line-associated blood stream infections—United States, 2001, 2008, and 2009. MMWR 2011;60:1-5
8. McGee DC, Gould MK: Preventing complications of central venous catheterization. NEJM 2003;348:1123-1133
9. Golden LR. Incidence and management of large-bore introducer sheath puncture of the carotid artery. J Cardiothorac Vasc Anesth 1995;9:425-428
10. Reuber M, Dunkley LA, Turton EP et al. Stroke after internal jugular venous cannulation. Acta Neurol Scand 2002;105:235-239
11. Ezaru CS, Mangione MP, Oravitz TM, et al. Eliminating arterial injury during central venous catheterization using manometry. Anesth Analg 2009;109:130-134
12. Safdar N, Maki DG. The pathogenesis of catheter-related bloodstream infection with noncufffed short-term central venous catheters. Intensive Care Med 2004;30:62-67
13. Berenholtz SM, Pronovost PJ, Lipsett PA, et al. Eliminating catheter-related bloodstream infections in the intensive care unit. Crit Care Med 2004; 32:2014-2020
14. Higuera F, Rosenthal VD, Duarte P, et al. The effect of process control on the incidence of central venous catheter-associated bloodstream infections and mortality in intensive care units in Mexico. Crit Care Med 2005; 33:2022-2027
15. Miller MR, Griswold M, Harris JM 2nd, et al. Decreasing PICU catheter-associated bloodstream infections: NACHRI's quality transformation efforts. Pediatrics 2010; 125:206-213
16. Warren DK, Cosgrove SE, Deikema DJ, et al. A multicenter intervention to prevent catheter-associated bloodstream infections. Infect Control Hosp Epidemiol 2006; 27:662-669
17. Sawyer M, Weeks K, Goeschel CA, et al. Using evidence, rigorous measurement, and collaboration to eliminate catheter-associated bloodstream infections. Crit Care Med 2010;38[Supp];S292-S298
18. Bansal R, Agarwal SK, Tiwari SC, et al. A prospective randomized study to compare ultrasound-guided with nonultrasound-guided double lumen internal
19. Cajozzo M, Quintini G, Cocchiera G, et al. Comparison of central venous catheterization with and without ultrasound guide. Transfus Apher Sci 2004; 31:199-202
20. Grebenik CR, Boyce A, Sinclair ME, et al. NICE guidelines for central venous catheterization in children. Is the evidence base sufficient? Br J Anaesth 2004; 92:827-830
21. Karakitsos D, Labropoulos N, De Groot E, et al. Real-time ultrasound-guided catheterisation of the internal jugular vein: a prospective comparison with the landmark technique in critical care patients. Crit Care 2006; 10:R162
22. Koroglu M, Demir M, Koroglu BK, et al. Percutaneous placement of central venous catheters: comparing the anatomical landmark method with the radiologically guided technique for central venous catheterization through the internal jugular vein in emergency hemodialysis patients. Acta Radiol 2006; 47:43-47
23. Mallory DL, McGee WT, Shawker TH: Ultrasound guidance improves the success rate of internal jugular vein cannulation: a prospective randomized trial. Chest 1990; 98:157-160
24. Slama M, Novara A, Safavian A, et al. Improvement of internal jugular vein cannulation using an ultrasound-guided technique. Intensive Care Med 1997; 23:916-919
25. Teichgraber UKM, Benter T, Gebel M et al. A sonographically guided technique for central venous access. AJR Am J Roentgenol. 1997; 169:731-733
26. Troianos CA, Jobes DR, Ellison N: Ultrasound-guided cannulation of the internal jugular vein: a prospective, randomized study. Anesth Analg 1991; 72:823-826
27. Verghese ST, McGill WA, Patel RI, et al. Comparison of three techniques for internal jugular vein cannulation in infants. Paediatr Anaesth 2000; 10:505-511
28. Verghese S, McGill W, Patel RI, et al. Ultrasound-guided internal jugular venous cannulation in infants: a prospective comparison with the traditional palpatation method. Anesthesiology 1999; 91:71-77
29. Rothchild, JM. Ultrasound guidance of central vein catheterization. In: On Making Health Care Safer: A critical analysis of patient safety practices. Rockvill, MD: AHRQ Publications; 2001; Chapter 21:245-255. Available at: http://archive.ahrq.gov/clinic/ptsafety/chap21.htm Accessed Feb 22, 2011
30. Revised statement on recommendations for uniform use of real-time ultrasound guidance for placement of central venous catheters. American College of Surgeons 2010. http://www.facs.org/fellows_info/statements/st-60.html Accessed Feb 22, 2011
31. Gillman LM, Blaivas M, Lord J, et al. Ultrasound confirmation of guide wire position may eliminate accidental arterial dilation during central venous cannulation. Scand J Trauma Resuscitation Emerg Med 2010;18:39-42
32. Stone MB, Hern HG. Inadvertent carotid artery cannulation during ultrasound guided central venous catheterization. Ann Emerg Med 2007;49:720
33. Sawchuck C, Fayad A: Confirmation of internal jugular guide wire position utilizing transesophageal echocardiography. Can J Anaesth 2001;48:688-690
34. Shah PM, Babu SC, Goyal A, et al. Arterial misplacement of large-caliber cannulas during jugular vein catheterization: case for surgical management. Am Coll Surg 2004;198:939-944

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

Pediatric anesthesia and analgesia outside of the OR: what you need to know

Pierre Fiset, MD, FRCPC
Pierre Fiset, MD, FRCPC, Head, Department of Anesthesia, Montreal Children's Hospital
Associate Professor, McGill University
Montréal, Canada

Provision of general anesthesia and deep sedation for children outside of the traditional operating room setting has become increasingly common in the past few years. Imaging and diagnostic techniques like MRI and endoscopy as well as performance of special procedures are often done under anesthesia in infants and children who cannot remain immobile or cannot tolerate the pain and discomfort as well as adult patients. Many factors have to be considered before considering to offer such a service. It is essential for the sedation/anaesthesia provider to have an adequate level of expertise and comfort in pediatric patient care. The hospital infrastructure must also be considered. The nature of care and services offered will be different in a community hospital, where the pediatric population is mixed with adults, versus a regional facility or a specialized pediatric institution. On the basis of safety, expertise of the staff and general organization of care, the hospital's administration as well as the Physicians Council must be involved and craft a clear policy to determine the nature of cases that will be allowed and those that should be referred to a more appropriate facility. In the present review course, we will cover the organization, safety requirements, patient selection and pediatric pharmacological aspects related to the administration of anesthesia to pediatric patients outside of the OR.

THE SPECTRUM OF SEDATION

The definition of sedation and its stratification into levels or stages has been controversial. Many scales have been proposed and considerable confusion arises in the terms used to qualify a given state of altered consciousness. The Ramsay sedation scale, its modified version, the OAA/S scale, the University of Michigan Sedation Scale and others have all been used to define clinical endpoints in numerous studies. An important breaking point on all those scales appears to be the border between a patient who is conscious and arousable, and one who becomes unconscious, with possible loss of airway reflexes and the ability to maintain adequate ventilation. Most people would accept that this defines the difference between "sedation" and "anesthesia", and that this dictates the level of expertise and qualifications of the sedation provider. Consequently, the acceptable dose ranges and the organisation of the sedation service will be determined by the desirable endpoint on the chosen sedation scale and the pharmacological knowledge on drugs to be used.

GENERAL ORGANIZATION

In any health care facility, a sedation committee should be instituted and should include anesthesiologists, nurses, respiratory therapists, pharmacists and all specialties requiring sedation for diagnostic and therapeutic procedures. The size of the hospital, the level of care provided (primary, secondary or tertiary) as well as the volume of patients will be considered in the choice of acceptable diagnostic and therapeutic procedures for sedation. Guidelines for the administration of sedation to pediatric patients have been published, among others by the American Pediatric Association, the American Society of Anesthesiologists and the American Emergency Medicine. Those guidelines define the standards for patient selection, evaluation and preparation, the equipement needed , the organization of the facility and the qualifications of the sedation providers. The administration of sedation which may progress to general anesthesia requires a minimum level or organization. The equipement required to safely perform anesthesia in a remote setting is very similar to what in required in a regular operating room. The administration of anesthetic gases often poses a problem, as scavenging is not always available. Resuscitation drugs and pediatric airway equipement must be immediately available. Recovery of pediatric patients in a mixed setting is challenging. Children are frequently agitated and require more supervision. They can be disturbing to other patients, so they should be recovered in a separate, dedicated area.

The personnel involved must be adequately trained in pediatric care and be familiar with the specific problems encountered with that population. All nursing and medical personnel should strongly consider PALS (Pediatric Advanced Life Support) training. In case of a major adverse event (respiratory or cardiac arrest) a code procedure must be in place in order to quickly get sufficient and pertinent support.

The department of anesthesia will determine which patients can be accepted on the basis of age, acuity and the level of training of practitioners. Many medical Societies have published guidelines on pediatric Anesthesia, including the ASA, the American Society of Pediatrics, the Royal College of Anaesthetists and all the major National Societies.

FACTORS ASSOCIATED WITH COMPLICATIONS

Many factors come into consideration in the determination of standard of practice in a specific hospital. Studies show that the incidence of respiratory and cardiac complications in pediatric anesthesia has decreased steadily over the past two decades.

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

Improvements in pharmacology, medical care and organization and patient selection have all been contributing to better care. A very young age (< 1 year old) and the presence of comorbidities impact negatively on outcome. The expertise of the practitioner and the number of pediatric cases done per year also seem to have an impact on outcome.

SPECIAL CONSIDERATIONS.

The features of Sedation outside of the OR are isolation of the sedation team, remote location, sometimes difficult access to the head and airway (MRI), and unavailability of immediate support in case of complications. Of course, in preparation for the procedure including in the ER, all fasting rules must be respected. In that context, the anaesthesiologist might opt for a more conservative approach for securing the airway using endotracheal intubation or an LMA. Caution should be exercised if spontaneous breathing is preserved in the absence of airway instrumentation, especially if the head is not readily accessible. Monitoring in any location is essentially the same as in the OR. Special considerations apply in some locations. For example in the MRI, vital signs are measured with special devices and transmitted wireless to remote monitors. In our institution, IV access is mandatory for any patient receiving sedation.

PHARMACOLOGIC AGENTS

Chloral hydrate

Still very popular for non painful radiological procedures, its effects are variable. It can cause airway obstruction and respiratory depression. In most settings, chloral hydrate will be used without an IV and without direct access to the head, leading to unfavourable resuscitation conditions.

ANESTHETIC VAPORS

Inhalation anesthesia is used is some locations provided scavenging can be made efficiently. Age related MAC and distribution variations are well known to anaesthesiologists.

Midazolam

Midazolam is widely used for sedation in children and adults. It induces dose related sedation and is suitable for a wide variety of procedures. Its onset is slightly delayed after IV administration, so escalating doses must be administered cautiously to avoid overdose by cumulation. As it does not possess analgesic properties, it is often used in combination with an opioid in painful procedures, with consequently a more likely progression to unconsciousness, respiratory depression and airway obstruction.

Fentanyl/remifentanil

Fentanyl and remifentanil are also widely used in off-site sedation/anesthesia settings. Fentanyl is mostly used in small bolus doses. Its pharmacology makes it difficult to maintain stable blood concentrations during an infusion. Remifentanil, on the other hand is much easier to titrate. It has a rapid onset and is metabolized by plasma and tissue esterases, so its offset is very short, a few minutes in infants and children. It is a μ opioid, with the same dose-related effects as fentanyl. Due to the predominance of their parasympathetic system, infants and children are very sensitive to the bradycardiac effects of remifentanil.

SPECIFIC ANTAGONISTS

Unexpected unconsciousness and respiratory depression are a consequence of synergistic interactions of benzodiazepines and opioids combined with interindividual pharmacologic variability. The possibility to immediately reverse the pharmacological effects of those agents with the specific antagonists flumazenil and naloxone provides a level of safety that is not available with agents like propofol.

Ketamine

Ketamine is very popular as a sole agent for sedation/analgesia in short painful procedures. There is considerable literature on its pharmacology and usage. This NMDA antagonist induces a unique dissociative state, intense analgesia, and preserves spontaneous respiration, airway reflexes and, in most circumstances, cardiovascular stability. The reported incidence of psychotropic effects varies significantly and its consequences are sometimes neglected or minimized. In busy centers where ketamine is often used for procedural sedation, a significant number of children report an unpleasant experience that can be long lasting.

Propofol

The pharmacological profile of propofol has been studied extensively in infants and children. It is widely used by anaesthesiologists to induce a predictable and controlable state of sedation. The pharmacodynamic profile of propofol is not age-dependant, as concentration-effect relationships are similar in infants, children and adults. However pharmacokinetics are influenced by age. Propofol is distributed more extensively to peripheral compartments so surprisingly higher doses and infusion rates (on a μg/kg basis) are needed in children to maintain an equivalent blood concentration, resulting in an equivalent effect. Context-sensitive half –time is increased in children, so the awakening is slower compared to adults. Titration of Propofol for infusion is easily done, although interindividual variability combined with the specifics of pediatric pharmacology can result in unexpected oversedation and airway obstruction. There is no specific antagonist for propofol, so unexpected overdosing needs to be addressed exclusively with direct support intervention on the airway and ventilation, sometimes for a prolonged period of time.

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

Dexmedetomidine

Dexmedetomidine is an α2 agonist acting mainly on central sympathetic receptors. It is not approved for use in children, but has been the subject of a significant number of recent studies on sedation in the ICU, adjunct to general anesthesia, treatment of emergence delirium and procedural sedation. It induces sedation in a dose dependant fashion, its effects on the central nervous system being very similar to REM sleep. Respiratory drive and airway protection are preserved, a definite advantage in procedural sedation. The onset of effect after a bolus dose and the termination of effect after ending the infusion are both rapid and reliable.

Despite all its favorable features, dexmedetomidine does not seem to be the "magic bullet", as case reports and studies have shown its ability to induce bradycardia and hypotension in children. More studies are underway, but dexmedetomidine could become a safer drug to use in procedural sedation.

CONCLUSION

Setting up and running a comprehensive pediatric sedation service must be based on evidence based information, wide consensus among providers and users and strict and safe protocols. There is an almost universal agreement on the principle that sedation must be administered by a dedicated, appropriately trained Health Professional. When infants and children are concerned, adequate knowledge of pediatric pharmacology and physiology is mandatory, and PALS training should definitely be encouraged.

REFERENCES

1. Kaplan RF, Cravero JP, Yaster M, Coté CJ. Sedation for Diagnostic and Therapeutic Procedures Outside the Opearating Room. In: Cote CJ, Lerman J, Todres I D, eds. A Practice of Anesthesia for Infants and Children, 4th Edition. Philadelphia: Saunders, 2009:1023-48.
2. American Academy of Pediatrics, American Academy of Pediatric Dentistry, Cote CJ, et al. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: an update. Pediatrics 2006;118:2587-602.
3. American Academy of Pediatrics, American Academy of Pediatric Dentistry, Cote CJ, et al. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: an update. Paediatric Anaesthesia 2008;18:9-10.
4. Engelhardt T, McCheyne AJ, Morton N, et al. Clinical adaptation of a pharmacokinetic model of Propofol plasma concentrations in children. Paediatric Anaesthesia 2008;18:235-9.
5. Mason KP. Sedation trends in the 21st century: the transition to dexmedetomidine for radiological imaging studies. [Review]. Paediatric Anaesthesia 2010;20:265-72.

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

Genomics: Why Do "Similar" Patients Have Different Outcomes?

Debra A Schwinn, MD
Professor & Chair, Department of Anesthesiology & Pain Medicine
Adjunct Professor of Pharmacology and Genome Sciences
University of Washington, Seattle, WA

Maren Kleine-Brueggeney, MD
Senior Fellow, University of Washington
Resident, Department of Anesthesiology & Pain Therapy, Bern, Switzerland
Department of Anesthesiology & Pain Medicine
University of Washington
Seattle, WA

Anush Oganesian, PhD
Research Assistant Professor
Department of Anesthesiology & Pain Medicine
University of Washington, Seattle, WA

ABSTRACT

Genetic variety is an important factor in why supposedly "similar" patients react differently to drugs as well as having different clinical outcomes. This review provides an update on concepts in modern genomic medicine, with emphasis on clinically relevant study approaches like candidate gene and genome wide association studies, and whole exon sequencing. The application of genomic medicine and its importance for rapid diagnosis of disease causing agents, as well clinical application in human tumor diagnosis/treatment and in cardiovascular disease are discussed. In addition to direct clinical applications, modern genomic approaches also play an important role in elucidating new mechanisms of disease.

INTRODUCTION

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

GENERAL DEFINITIONS

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

"Omics": After sequencing the entire human DNA of a few individuals in 2000, scientists turned to massively producing DNA sequences from individual patients with and without disease. Such massive screening of DNA is termed "genomics" and studies using these large-scale efforts, clinical genomics. The next large scale tool to be added to the genomics toolbox were large arrays consisting of thousands of single stranded RNA molecules, or fragments of such RNA, from cells or animal/human tissues. By comparing before/after conditions, changes in RNA quantities could be examined. Large-scale protein analysis has been more difficult technically since it involves predominantly the use of mass spectroscopy which is more labor intensive; this field is called proteomics. Following

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

suit, identification of hundreds of small molecules and metabolites in cells, predominantly by old-fashioned biochemistry methodologies, is called metabolomics. Since DNA is by far the easiest and cheapest of these methods, many studies using DNA sequencing surfaced first, with RNA microarrays running a close second historically. From these 2 methods, fingerprints of the genomics of tumors and diseases in patients have begun to be derived. Ironically, however, the most logical way to examine diseases would be to start with metabolomics, since this is the milieu that is most often changed with disease or acute insults. By understanding alterations in proteins and metabolites, a true signature of biomarkers is obtained. RNA microarrays can then be used to determine the mechanism and/or pathway by which such diseases occurred (rather than being primarily a diagnostic tool itself), particularly given the unstable nature of RNA in general. DNA alterations can ultimately be used as an inexpensive screening tool once such variation is linked with protein/metabolite change.

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

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

MicroRNA: Adding complexity to gene regulation is the recent discovery of microRNAs (miRNAs) and other longer non-coding RNAs. miRNAs are small 18–25 nucleotide long non-coding RNAs that modulate gene expression levels in a sequence-specific manner via the binding of mature miRNAs to complementary mRNAs. This binding negatively regulates expression of specific genes by either degrading the bound target mRNA or directly inhibiting translation. Specific miRNAs have been implicated in cell differentiation, cell apoptosis/death, ischemia/reperfusion responses, fat metabolism, and carcinogenesis in various species.[1,2] Presence/absence of specific miRNAs in tumors has been hypothesized to potentially predict clinical outcome with tumor resection/treatment and ultimate clinical outcome, although one recent study in non-small cell lung cancer suggests no predictive ability.[3] miRNAs also play a critical role in controlling cardiac stress responses that lead to transcriptional and translational alterations in gene expression. Over-expression of various miRNAs in cardiomyocytes *in vitro* induces cardiac hypertrophy and overexpression of miR-195, a known stress-inducible miRNA, resulting in abnormal cardiac remodeling and heart failure in transgenic mice.[4] These findings suggest that miRNAs are important regulators of cardiac function and represent potential therapeutic targets for heart disease.

UPDATE ON CLINICAL GENOMIC STUDY METHODS

Candidate gene association studies: The modern historical standard for clinical genetics studies is the association study where incidence of DNA genetic variants (predominantly SNPs in a few candidate genes), is examined between groups of patients with and without a disease. Such studies require careful matching for clinical co-variants such as presence/absence of chronic disease, active medications, population stratification (race, country of origin), age, sex, clinical intervention details, etc. While such studies have been powerful, they are notoriously difficult to replicate, requiring large numbers of patients and crisp definitions of clinical outcomes (which are sometimes difficult to assure from medical records alone). In addition, even when SNPs from several genes are examined, and interactions considered, ultimately investigators "guess" which genes may be most important in a disease and use those as the starting point. As has been pointed out by many, this introduces bias in that only "known" genes/pathways

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

are considered rather than all possible mechanisms. As a result, targeted candidate association studies alone are increasingly hard to publish unless replication in a separate group of individuals and/or associated biologic changes can be reported in the same study.

GWAS studies: Genome wide association studies (GWAS; described initially above) also examine groups of patients with/without disease. But rather than examining targeted SNPs from a selected group of genes, GWAS specifically takes an unbiased approach by using thousands of GWAS markers spread across the entire genome. The theoretical advantage of such an approach is that novel pathways/genes can be elucidated that may be important in either predicting disease or providing mechanistic insights. As with targeted association studies, large populations of patients must be studied, both cases and controls. This has been difficult since GWAS panels containing thousands of genes per patients are quite expensive. Also, even though thousands of SNPs are examined, this still means that potentially only 1 per 10,000 DNA nucleotides are studied. Since not all genetic variation is present in haplotypes with a study marker, or related to the marker SNP by linkage disequilibrium, then important genetic variability can be missed. Hence this approach should be considered a first "low hanging fruit" approach where a positive may be meaningful for common genetic variants, but a negative result may not be helpful. Indeed, some have argued that large GWAS studies in hypertension, even those with >30,000 individuals studied, have neither illuminated key genes with significant biologic effects nor unlocked the genetic basis of the disease.[5] One conclusion from these studies is that rare genetic variants may play a bigger role in "common" disease than was originally thought.

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

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

DIAGNOSING PRESENCE OF DISEASE CAUSING AGENTS

One area where medicine and anesthesiology have benefited dramatically from genomic medicine advances is in diagnosis of pathogens causing disease. This is especially true in the intensive care unit where presence of bacteria and viruses can be identified rapidly, including specific strains. This is possible using diagnostic amplification of small fragments of DNA from these invading organisms. While normal flora must be taken into account, drug-resistant and highly virulent strains of bacteria can be identified now fairly rapidly, enabling treatment to be definitively initiated within hours of specimen testing.[6,7] Diagnostic cultures often take several days, and can still be used for confirmation, but in many cases a more definitive anti-microbial agent can be started immediately. This decreases drug resistance within hospitals (by decreasing the use of broad-spectrum antibacterial agents) and helps to track strains present within outbreaks.

In the outpatient setting, diagnosis of sexually transmitted diseases has also been greatly enhanced using molecular genetic approaches to diagnose presence and virulence of specific strains. Recent discoveries suggest a new mechanism of sexually transmitted disease may be infection by non-viral *Trichomonas vaginalis* which may itself be infected with up to 4 distinct strains of viral DNA, complicating overall disease expression.[8] This type of information is crucial for modern day public health tracking and interventions.

Chronic disease patients also benefit from examination of pathologic infectious agents. For example, patients with cystic fibrosis often have gram negative lung infections since they have difficulty clearing their thick mucous secretions. A recent study examined the role of specific strains of *Pseudomonas Aeruginosa* in patients with cystic fibrosis and demonstrated that a common strain (Liverpool epidemic strain) is associated in England, Australia, and Canada with worse lung function, death and/or need for lung transplantation in this vulnerable population of patients.[9] This information then provides

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

the opportunity to intervene in such patients more rigorously.

CURRENT CLINICAL HUMAN DISEASE APPLICATIONS

Tumor diagnosis and treatment: Traditionally, tumor diagnosis has been accomplished using histology and pathologic methods. Such approaches have increasingly relied on antibodies capable of identifying tumor markers, which generally are proteins uniquely expressed in tumor cells and not host tissue cells. However, since the genomic revolution, it has been recognized that genetic abnormalities in cells that ultimately go on to become cancerous can be harnessed for diagnosis and prediction of treatment options and efficacy. This has been true of childhood tumors for almost 2 decades since isolation of tumor cells in blood is rather easily available.[10] However, it is a harder prospect for solid tumors. Hence new molecular findings relating molecular markers (predominantly DNA deletions and mutations) for specific brain tumors (gliomas) is encouraging since they appear to facilitate diagnosis, management, and predict outcome in low-grade gliomas.[11] In addition, in other studies involving neuroblastoma, the important prognostic role of the ABCC1 (ATP-binding cassetted sub-family C member1) gene in patient outcome has recently been suggested.[12] Another example is breast cancer where BRCA gene mutations are well known to increase risk of breast cancer in a subpopulation of patients, yet the majority of breast cancers without BRCA mutations remain difficult to categorize and, in the cases, treat.13 Molecular genetics of tumors is an important growth area in medicine and may be able to finally unlock adult solid tumors to the point of having better response to therapeutic intervention and ultimately better outcomes.

Cardiovascular disease: Many aspects of cardiovascular disease have a genetic component, ranging from coronary disease,[14] to familial peripheral arterial calcification,15 blood coagulation,[16-18] cardiovascular drug action. Even chronic inflammation, known to be important in the acquisition and progression of cardiovascular disease, has been examined in terms of "inflammasome-mediated disease.19 In this review we highlight one example of a commonly used clinical genetics approach to two types of anti-coagulation.

One of the more thoroughly investigated areas where genomic approaches have real impact on clinical practice is in the area of coagulation, specifically prediction of starting dose for highly toxic drugs such as warfarin (coumadin)[16] and use/efficacy of anti-platelet drugs such as clopidogrel.[17,18] In these settings, genetic testing can reveal opposite situations. For warfarin, gentoypes for warfarin and vitamin K metabolism (e.g. genotype variables included P450 metabolizing enzymes CYP2C9 and CYP4F2, as well as vitamin K VKORC1) have been shown to be important in improving prediction of therapeutic warfarin dose and overall anticoagulation management versus standard clinical approaches.[16] Because the improved prediction has great potential to limit warfarin side-effects such as excessive bleeding and emergency room visits, genetic testing is becoming more routine as warfarin is initiated. For clopidogrel it is usually therapeutic efficacy, rather than side-effects, that is tested. In this case, individuals with specific genetic variants do not respond to the drug and therefore the expected anti-platelet activity is not present. This results in lack of protection from myocardial infarction in the setting of unstable angina or interventions such as coronary artery stent placement. This risk is considered so high, and clopidogrel so common in this important clinical setting, that the FDA recently put a black box warning so that clinicians would be aware to prescribe alternative anti-platelet drugs to the subset of patients who are non-responders.

Transplantation: Because genetic variation exists in molecules regulating innate and adaptive immunity, organ transplantation has become an area where genetic approaches are becoming increasingly considered. Genetic variants in this setting can have important effects in both organ preservation (e.g. sufficient immunosuppression to prevent rejection) and drug side effects (e.g. limiting immunosuppression side-effects such as infection, metabolic derangements, and renal injury). These effects include immune system modulation as well as drug metabolism pathways (e.g. CYP3A5 for tacrolimus dosing). Taken together, effects on acute rejection, delayed graft function, long-term allograft dysfunction and mortality, post-transplant metabolic complications, and recurrent disease are affected by many known genetic variants, specific for each phase of transplantation long-term success. Genetic variants and mRNA profiling that can be used for screening purposes,[20] as well as future visions for how genomics can add value in this unique area of medicine, have been summarized in several recent reviews.[21-23]

GENETIC VARIANTS REVEAL NEW MECHANISMS OF DISEASE

Alpha1-adrenergic receptors (α1AR) are G protein-coupled transmembrane receptors that mediate actions of the sympathetic nervous system through binding of endogenous catecholamines epinephrine and norepinephrine (NE). Among the 3 α1ARs subtypes, α_{1a}ARs predominate in human vascular smooth muscle, particularly in resistant vessels.[24,25] Vasoconstriction and vascular remodeling are precipitating factors in human hypertension, a major cardiovascular risk factor for developing heart disease and stroke. Stress-induced development of hypertrophy is characterized by changes in the structure of both blood vessels and heart. Recently it has been found that a genetic variant present in the 3rd intracellular loop of the human α1aAR constitutively couples to a distinct biochemical pathway with enhanced cellular growth effects.[26] Such findings suggest that by discovering new pathways activated by genetic variants in physiological pathways, entirely new drug classes may be able to be considered in the treatment of common diseases such as hypertension.

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

CONCLUSION

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

REFERENCES

1. Schickel R, Boyerinas B, Park SM, Peter ME. MicroRNAs: key players in the immune system, differentiation, tumorigenesis and cell death. Oncogene 2008;27:5959-74.
2. Lee Y, Kim M, Han J, et al. MicroRNA genes are transcribed by RNA polymerase II. EMBO J 2004;23:4051-60.
3. Voortman J, Goto A, Mendiboure J, et al. MicroRNA expression and clinical outcomes in patients treated with adjuvant chemotherapy after complete resection of non-small cell lung carcinoma. Cancer Res 2010;70:8288-98.
4. Busk PK, Cirera S. MicroRNA profiling in early hypertrophic growth of the left ventricle in rats. Biochem Biophys Res Commun 2010;396:989-93.
5. Kurtz TW. Genome-wide association studies will unlock the genetic basis of hypertension.: con side of the argument. Hypertension 2010;56:1021-5.
6. Josko D. Molecular bacteriology in the clinical laboratory. Clin Lab Sci 2010;23:237-41.
7. Josko D. Molecular virology in the clinical laboratory. Clin Lab Sci 2010;23:231-6.
8. Goodman RP, Freret TS, Kula T, et al. Clinical Isolates of Trichomonas vaginalis Concurrently Infected by Strains of Up to Four Trichomonasvirus Species (Family Totiviridae). J Virol 2011;85:4258-70.
9. Aaron SD, Vandemheen KL, Ramotar K, et al. Infection with transmissible strains of Pseudomonas aeruginosa and clinical outcomes in adults with cystic fibrosis. JAMA 2010;304:2145-53.
10. Gentles AJ, Plevritis SK, Majeti R, Alizadeh AA. Association of a leukemic stem cell gene expression signature with clinical outcomes in acute myeloid leukemia. JAMA 2010;304:2706-15.
11. Bourne TD, Schiff D. Update on molecular findings, management and outcome in low-grade gliomas. Nat Rev Neurol 2010;6:695-701.
12. Pajic M, Murray J, Marshall GM, Cole SP, Norris MD, Haber M. ABCC1 G2012T single nucleotide polymorphism is associated with patient outcome in primary neuroblastoma and altered stability of the ABCC1 gene transcript. Pharmacogenet Genomics 2011;21:270-9.
13. Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. N Engl J Med 2010;363:1938-48.
14. Wang AZ, Li L, Zhang B, Shen GQ, Wang QK. Association of SNP rs17465637 on Chromosome 1q41 and rs599839 on 1p13.3 with Myocardial Infarction in an American Caucasian Population. Ann Hum Genet 2011.
15. St Hilaire C, Ziegler SG, Markello TC, et al. NT5E mutations and arterial calcifications. N Engl J Med 2011;364:432-42.
16. Burmester JK, Berg RL, Yale SH, et al. A randomized controlled trial of genotype-based Coumadin initiation. Genet Med 2011.
17. Gladding P, Panattoni L, Webster M, Cho L, Ellis S. Clopidogrel pharmacogenomics: next steps: a clinical algorithm, gene-gene interactions, and an elusive outcomes trial. JACC Cardiovasc Interv 2010;3:995-1000.
18. Wang L, McLeod HL, Weinshilboum RM. Genomics and drug response. N Engl J Med 2011;364:1144-53.
19. Hoffman HM, Brydges SD. Genetic and Molecular Basis of Inflammasome-mediated Disease. J Biol Chem 2011;286:10889-96.
20. Pham MX, Teuteberg JJ, Kfoury AG, et al. Gene-expression profiling for rejection surveillance after cardiac transplantation. N Engl J Med 2010;362:1890-900.
21. Kruger B, Schroppel B. Genetic variations and transplant outcomes. Nephron Clin Pract 2011;118:c49-54.
22. Naesens M, Sarwal MM. Molecular diagnostics in transplantation. Nat Rev Nephrol 2010;6:614-28.
23. Ohmann EL, Brooks MM, Webber SA, et al. Association of genetic polymorphisms and risk of late post-transplantation infection in pediatric heart recipients. J Heart Lung Transplant 2010;29:1342-51.
24. Autelitano DJ, Woodcock EA. Selective activation of alpha1A-adrenergic receptors in neonatal cardiac myocytes is sufficient to cause hypertrophy and differential regulation of alpha1-adrenergic receptor subtype mRNAs. J Mol Cell Cardiol 1998;30:1515-23.
25. Rudner XL, Berkowitz DE, Booth JV, et al. Subtype specific regulation of human vascular alpha(1)-adrenergic receptors by vessel bed and age. Circulation 1999;100:2336-43.
26. Oganesian A, Darbinyan I, Schwinn DA. Constitutive coupling of a naturally occurring human alpha1aAR genetic variant to MMP/EGFR transactivation pathway. American Society of Biochemistry and Molecular Biology 2011 Abstract 751.12.

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

Updates in Neuroanesthesiology

George A. Mashour, MD, PhD
Director, Division of Neuroanesthesiology, Assistant Professor of Anesthesiology & Neurosurgery
Faculty, Neuroscience Graduate Program
University of Michigan Medical School, Ann Arbor, MI

OBJECTIVES:

At the end of this lecture, the participant should be able to:

1. make informed decisions regarding use of intravenous vs. inhalational anesthetics during craniotomy.
2. articulate the controversy regarding the use of dexmedetomidine in patients with neurologic injury.
3. identify the potential advantages of hypertonic saline over mannitol for brain relaxation.
4. calculate an effective dose of adenosine to achieve 60 seconds of hypotension during aneurysm clipping.
5. make informed decisions regarding neuroprotective strategies during temporary aneurysm clipping.
6. describe the long-term benefits of scalp block for post-craniotomy analgesia.

INTRODUCTION AND FORMAT

Neuroanesthesiology involves the perioperative care of patients with neurologic disease undergoing surgical intervention. The breadth of neurosurgical practice (from major spine, to cerebrovascular surgery, to awake craniotomy) and neuroscientific investigation could potentially lead to an unwieldy update lecture. As such, the current lecture will be structured around a single clinical case of a patient with subarachnoid hemorrhage presenting for clipping of a ruptured intracranial aneurysm. The case discussion will draw upon recent literature from the past several years as a method of informing clinical decision making. The advantages of this case-based approach are greater coherence and focus; the disadvantage is that other important topics (such as spine or functional neurosurgery) will be excluded. It is hoped that this format will be high-yield for a relatively brief lecture intended to help the participant understand both the fundamentals and current trends of neuroanesthetic practice.

CASE DESCRIPTION

The patient was a 30-year old female with no significant past medical history who was found unresponsive by her father. Two days prior to admission the patient had complained of a headache, which had resolved; on the day of admission she missed work without calling, which prompted further investigation by her family. Of note, her grandfather died of a ruptured intracranial aneurysm. Computed tomography from an outside hospital revealed diffuse subarachnoid hemorrhage and a lesion suspicious for an intracranial aneurysm (Figure 1); subsequent angiography at our institution identified a giant (2.5cm diameter) right middle cerebral artery aneurysm (Figure 2). Due to the size of the aneurysm, coiling was not considered a feasible option and surgical clipping was indicated. *You are the on-call anesthesiologist assigned to the case!*

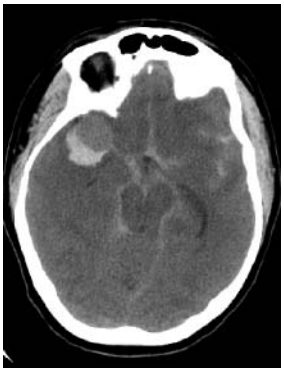


Figure 1: Head computed tomography from outside hospital revealing diffuse subarachnoid hemorrhage.

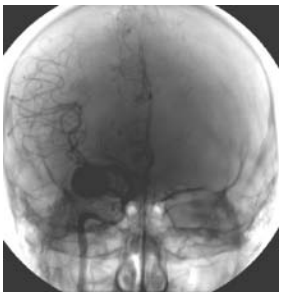


Figure 2: Diagnostic angiogram revealing giant right middle cerebral artery aneurysm.

CASE DISCUSSION

The following discussion is organized around a series of questions that are pertinent to the management of this case, as well as craniotomies in general. The "answers" to each question are derived from recent articles in the field of neuroanesthesiology.

Is there an advantage to intravenous vs. inhalational anesthesia?

Lauta *et al*.[1] conducted a randomized controlled trial to test the hypothesis that a sevoflurane-remifentanil anesthetic was superior to a propofol-remifentanil anesthetic in adult patients undergoing supratentorial craniotomy. There were approximately 150 patients in each group. Sevoflurane was administered at 0.7-2.0% whereas propofol was infused at 6-10 mg/kg/hr. The primary outcome was the time to return to an Aldrete score of ≥9 during the 3 hours after surgery, an endpoint based on Todd et al, 1993.[2] Secondary outcomes included time to eyes open, extubation time, adverse events, intraoperative hemodynamics, opioid consumption, and brain relaxation score. There was no difference in the primary outcome between the sevoflurane and propofol groups. Time to eyes open and extubation were significantly shorter in the sevoflurane group, but only by approximately 2 minutes for each group.

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

The authors conclude that sevoflurane is not clinically superior to a propofol anesthetic. The decision to use intravenous vs. inhalational anesthesia in the current patient should therefore be dictated by the underlying physiology. Intravenous agents such as propofol may be advantageous in that there remains a tightly coupled decrease of cerebral blood flow in response to decreased cerebral metabolic rate. In this patient, a reduction in cerebral blood flow, cerebral blood volume, and intracranial pressure may be beneficial. Metabolism-flow coupling occurs with sevoflurane, but the ratio is altered due to the cerebral vasodilation caused by potent inhalational agents.

Is it safe to use dexmedetomidine in a patient with neurologic injury?

The alpha-2 agonist dexmedetomidine has many potential advantages for the neurosurgical patient undergoing aneurysm clipping, including sympatholysis and a minimum alveolar concentration-sparing effect. However, prior studies in canines have suggested that dexmedetomidine has a cerebral vasoconstrictive effect that is not associated with a coupled reduction in cerebral metabolic rate.[3,4] In a patient with neurologic insult, this would imply a reduction in much-needed supply without a concomitant reduction in demand, with potentially deleterious effects. However, a recent study in nonanesthetized human volunteers suggested a coupled decrease in cerebral blood flow and metabolism.[5] In 2010, a follow-up report was published on anesthetized humans undergoing cerebrovascular surgery who also had concomitant brain parenchymal O_2 measurement.[6] Brain tissue probes were placed in regions at risk of impaired perfusion. Dexmedetomidine was bolused at 1mcg/kg and then infused at 0.5-0.7 mcg/kg/h. Parenchymal O_2 measurements were stable after dexmedetomidine infusion. In conjunction with past findings in humans, the current study does not support an adverse cerebral vasoconstrictive effect of dexmedetomidine that is independent of a reduction in cerebral metabolic rate.

The brain is "tight"—is there any advantage to using hypertonic saline vs. mannitol?

In 2007, Rozet and colleagues conducted a blinded, randomized controlled trial in 40 patients undergoing craniotomy in order to compare equiosmolar mannitol and 3% saline.[7] The investigators found that the two osmotic agents were comparable in achieving brain relaxation (using a four-point scale: 1-perfectly relaxed, 2-satisfactorily relaxed, 3=firm, 4=bulging). Mannitol was associated with increased urine output and rising lactate levels compared to 3% saline. In 2010, Wu *et al.* conducted a larger trial of supratentorial craniotomy in which 122 patients were randomized to 3% saline and 116 patients were randomized to mannitol.[8] The Wu *et al.* study demonstrated that 3% saline was more effective at achieving brain relaxation (using a three-point scale: 1-tight, 2-adequate, 3-soft). Like the Rozet *et al.* study, Wu and colleagues found that mannitol was associated with significantly more urine output. Both studies found that 3% saline increased serum sodium and mannitol decreased serum sodium. Hypertonic saline may therefore have advantages as an osmotic agent for brain relaxation and maintenance of fluid balance.

How much adenosine should I use to facilitate aneurysm clipping or in the event of rupture?

Adenosine is a purine nucleoside that slows conduction through the atrioventricular node and has a negative chronotropic effect at the sinoatrial node. Retrospective clinical reports in 2010 by Bebawy and colleagues[9] and 2011 by Guinn and colleagues[10] have contributed to our understanding of adenosine dosing to facilitate surgical management of complex aneurysms. Bebawy *et al.* reviewed cases over a 3-year period in which adenosine was used to facilitate intracranial aneurysm clipping. Patients were not given adenosine if they had significant coronary artery disease (left main >80% stenosed, multi-vessel disease), conduction defects, pacemakers, or severe reactive airway disease. In order to achieve systolic blood pressure <60mmHg for approximately 60 seconds, a median dose of 0.34mg/kg ideal body weight was used during propofol-induced burst suppression. This also resulted in systolic blood pressure less than baseline for approximately 2 minutes. Of the 24 patients who received adenosine, 2 developed stable intraoperative atrial fibrillation and 2 other patients developed mild troponin elevation. The study by Guinn *et al.* was also retrospective and evaluated 27 patients over 2 years who received adenosine. A median dose of 0.53mg/kg was associated with systolic blood pressure <60mmHg for 60-90 seconds; this was not dosed to ideal body weight. Both articles suggested that pacing pads be placed after induction and prior to the use of adenosine, given the reported 4% incidence of temporary pacing required in a study of endovascular aortic aneurysm repair.[11] Taken together, these studies suggest that an adenosine dose of approximately 0.4mg/kg may be needed to achieve the hemodynamic conditions required for aneurysm clipping.

Will cooling or pharmacologic interventions during temporary clipping improve outcome?

Before permanent clipping of an intracranial aneurysm, a temporary clip is often placed on the parent vessel. The advantage of the temporary clip is that it allows the surgeon to manipulate the aneurysm without fear of rupture; the disadvantage is that this "proximal control" can potentially result in focal cerebral ischemia in the brain parenchyma normally supplied by the clipped vessel. Thus, a neuroprotective intervention that could reduce the risk of cerebral ischemia during temporary clipping would be of clinical benefit. Techniques that have been employed for this purpose include mild hypothermia, titration of an intravenous anesthetic to burst suppression, and induced hypertension for improved collateral flow. In 2010, Hindman and colleagues[12] published a secondary analysis of the Intraoperative Hypothermia for

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

Aneurysm Surgery Trial (IHAST).[13] IHAST found that mild hypothermia (33°C) did not improve neurologic or neuropsychologic outcome in patients who underwent surgical clipping of a ruptured intracranial aneurysm. However, cases in which temporary clipping occurred were not analyzed separately in the original study. Of those receiving temporary clipping in IHAST (n=441), there were 208 patients assigned to intraoperative hypothermia and 233 patients to normothermia. Furthermore, of the 441 patients, 263 received no additional protective intervention and 178 did (157=thiopental, 20=etomidate, 1=other). The main findings of Hindman *et al.* were that neither mild hypothermia nor supplemental pharmacologic intervention had any meaningful association with early or late neurologic outcome in the setting of temporary clipping. Of note, longer temporary clip times (>20 minutes) were associated with less favorable outcomes.

Will scalp block facilitate postoperative pain control?

Despite common misconceptions, craniotomies can be painful and can lead to chronic pain.[14] In 2009, Batoz *et al*. published the results of a randomized study in which patients undergoing craniotomy received scalp infiltration with ropivacaine 0.75% vs. a control condition without.[15] Intravenous acetaminophen and nalbuphine were administered for postoperative pain control in both groups. The primary outcome was nalbuphine consumption, with secondary outcomes including visual analog pain scale scores in the postoperative period, as well as persistent and neuropathic pain at 2 months. There was no statistically significant reduction in nalbuphine consumption, but the group receiving scalp block had significantly reduced pain scores in the 24 hours following surgery. At 2 months, however, the group receiving scalp block had significantly lower persistent pain (8%) and neuropathic pain (4%) compared to the control group (56% and 25%, respectively). Osborn and Sebeo have authored an excellent article reviewing the technique of scalp block.[16] Scalp blocks may be beneficial because even non-opioid analgesic options such as gabapentin, although efficacious, can delay extubation and be associated with increased postoperative sedation.[17]

CONCLUSION

The patient in this case received adenosine boluses and temporary clipping during a total intravenous anesthetic and had her aneurysm successfully clipped despite technical challenges—she is now making an excellent recovery. This case served as a vehicle to discuss several recent studies related to cerebrovascular surgery and craniotomy in general. For a comprehensive update in neuroanesthesiology, the reader is referred to the excellent annual review article by Pasternak and Lanier.[18]

REFERENCES

1. Lauta E, Abbinante C, Del Gaudio A, Aloj F, Fanelli M, de Vivo P, Tommasino C, Fiore T. Emergence times are similar with sevoflurane and total intravenous anesthesia: results of a multicenter RCT of patients scheduled for elective supratentorial craniotomy. J Neurosurg Anesthesiol 2010;22:110-8
2. Todd MM, Warner DS, Sokoll MD, Maktabi MA, Hindman BJ, Scamman FL, Kirschner J. A prospective, comparative trial of three anesthetics for elective supratentorial craniotomy. Propofol/fentanyl, isoflurane/nitrous oxide, and fentanyl/nitrous oxide. Anesthesiology 1993;78:1005-20
3. Karlsson BR, Forsman M, Roald OK, Heier MS, Steen PA. Effect of dexmedetomidine, a selective and potent alpha 2-agonist, on cerebral blood flow and oxygen consumption during halothane anesthesia in dogs. Anesth Analg 1990;71:125-9
4. Zornow MH, Fleischer JE, Scheller MS, Nakakimura K, Drummond JC. Dexmedetomidine, an alpha 2-adrenergic agonist, decreases cerebral blood flow in the isoflurane-anesthetized dog. Anesth Analg 1990;70:624-30
5. Drummond JC, Dao AV, Roth DM, Cheng C-R, Atwater BI, Minokadeh A, Pasco LC, Patel PM. Effect of dexmedetomidine on cerebral blood flow velocity, cerebral metabolic rate, and carbon dioxide response in normal humans. Anesthesiology 2008;108:225-32
6. Drummond JC, Sturaitis MK. Brain tissue oxygenation during dexmedetomidine administration in surgical patients with neurovascular injuries. J Neurosurg Anesthesiol 2010;22:336-41
7. Rozet I, Tontisirin N, Muangman S, Vavilala MS, Souter MJ, Lee LA, Kincaid MS, Britz GW, Lam AM. Effect of equiosmolar solutions of mannitol versus hypertonic saline on intraoperative brain relaxation and electrolyte balance. Anesthesiology 2007;107:697-704
8. Wu C-T, Chen L-C, Kuo C-P, Ju D-T, Borel CO, Cherng C-H, Wong C-S. A comparison of 3% hypertonic saline and mannitol for brain relaxation during elective supratentorial brain tumor surgery. Anesth Analg 2010;110:903-7
9. Bebawy JF, Gupta DK, Bendok BR, Hemmer LB, Zeeni C, Avram MJ, Batjer HH, Koht A. Adenosine-induced flow arrest to facilitate intracranial aneurysm clip ligation: dose-response data and safety profile. Anesth Analg 2010;110:1406-11
10. Guinn NR, McDonagh DL, Borel CO, Wright DR, Zomorodi AR, Powers CJ, Warner DS, Lam AM, Britz GW. Adenosine-induced transient asystole for intracranial aneurysm surgery: a retrospective review. J Neurosurg Anesthesiol 2011;23:35-40
11. Kahn RA, Moskowitz DM, Marin ML, Hollier LH, Parsons R, Teodorescu V, McLaughlin M. Safety and efficacy of high-dose adenosine-induced asystole during endovascular AAA repair. J Endovasc Ther 2000;7:292-6
12. Hindman BJ, Bayman EO, Pfisterer WK, Torner JC, Todd MM. No association between intraoperative hypothermia or supplemental protective drug and neurologic outcomes in patients undergoing temporary clipping during cerebral aneurysm surgery: findings from the Intraoperative Hypothermia for Aneurysm Surgery Trial. Anesthesiology 2010;112:86-101
13. Todd MM, Hindman BJ, Clarke WR, Torner JC. Mild intraoperative hypothermia during surgery for intracranial aneurysm. N Engl J Med 2005;352:135-45
14. Schaller B, Baumann A. Headache after removal of vestibular schwannoma via the retrosigmoid approach: a long-term follow-up-study. Otolaryngol Head Neck Surg 2003;128:387-95
15. Batoz H, Verdonck O, Pellerin C, Roux G, Maurette P. The analgesic properties of scalp infiltrations with ropivacaine after intracranial tumoral resection. Anesth Analg 2009;109:240-4
16. Osborn I, Sebeo J. "Scalp block" during craniotomy: a classic technique revisited. J Neurosurg Anesthesiol 2010;22:187-94
17. Ture H, Sayin M, Karlikaya G, Bingol CA, Aykac B, Ture U. The analgesic effect of gabapentin as a prophylactic anticonvulsant drug on postcraniotomy pain: a prospective randomized study. Anesth Analg 2009;109:1625-31
18. Pasternak JJ, Lanier WL. Neuroanesthesiology update 2010. J Neurosurg Anesthesiol 2011;23:67-99

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

Multimodal Analgesia for Perioperative Pain Management

Asokumar Buvanendran, MD
Professor, Department of Anesthesiology, Director of Orthopedic Anesthesia
Rush University Medical Center, Chicago, IL

Multimodal analgesia captures the effectiveness of individual agents in optimal dosages that maximize efficacy and attempts to minimize side effects from one analgesic (mainly opioids). This important concept employs the theory that agents with different mechanisms of analgesia that may have synergistic effects in preventing or treating acute pain when used in combination. These regimens must be tailored to individual patients, keeping in mind the procedure being performed, side effects of individual medications, and patients' pre-existing medical conditions.[1] The concept and theory of multimodal analgesia is not new; however several novel pharmacological agents have emerged and can be added to the drugs that can be used in this fashion. It is vital to realize that blocking the neuronal pathway during surgery with local anesthetics does not decrease the humeral biochemical responses that occur during surgery which have to be inhibited by administering systemic pharmacological therapy.[2] This abstract will only focus on the recent advances in pharmacological agents for multimodal therapy.

ACETAMINOPHEN

Oral acetaminophen has been used for several decades[3] and Paracetamol, an intravenous formulation of acetaminophen, became available in 2002 and has been studied in Europe. Görögcs and colleagues administered a single dose of 1 gram of intravenous paracetamol (Perfalgan®) prior to the termination of surgery and observed high patient satisfaction and good tolerance of the drug in 601 patients undergoing minor outpatient surgical procedures.[4] Nearly half of these patients (42.7 %) received the single dose of paracetamol as monotherapy for post-operative pain. Salihglu, et al. randomized 40 patients undergoing laparoscopic cholecystectomy to 1 gram paracetamol (after intubation and prior to incision) or saline infusion. Significant improvements in outcomes in the paracetamol group included lower VAS, lower morphine consumption, and shorter stay in the recovery room (32 ± 11 versus 48 ± 14 minutes.)[5] Approved by the United States FDA in November 2010, intravenous (IV) acetaminophen (Ofirmev®) has been studied and shown to be safe. IV acetaminophen endorses a quick onset with meaningful pain relief achieved 25 minutes after administration in patients undergoing laparoscopic surgery,[6] 25-27 minutes after total hip arthroplasty. [7] Ender, et al. retrospectively evaluated the use of a fast-track protocol (which included IV acetaminophen) for cardiac surgery in 421 patients compared to matched controls that were not fast-tracked and did not receive IV acetaminophen.[8] The oral administration of acetaminophen can probably achieve the same results as IV acetaminophen in patients who have a functioning gastrointestinal system. However it is also to be noted that the analgesic effect is much more rapid than oral due to the pharmacokinetics.

Combinations of acetaminophen and non steroidal anti-inflammatory drugs (NSAIDs) have been investigated and may offer enhanced effects as based on current research. In 55 children undergoing hernia repair, 30 mg ketorolac and 20 mg/kg acetaminophen resulted in significantly lower post-operative fentanyl consumption, less sedation and vomiting.[9] A systematic review of this subject determined that when used as a combination, NSAIDs and paracetamol "offer superior analgesia compared with either drug alone[10] and 18/21 studies included had positive results with regard to lowering visual analogue score (VAS) and/or use of rescue analgesics. The combination was more effective than paracetamol (85 % of studies) or NSAIDs (64 % of studies) as individual agents.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

The use of NSAID use in the perioperative period has been well established taking into consideration the adverse effects of bleeding. The utility of COX-2 inhibitors in this scenario has been demonstrated to be a benefit.[1,2] Randomized, double-blind, placebo-controlled study to examine celecoxib 200mg versus placebo in patients undergoing major plastic surgery demonstrated the ability of celecoxib to reduce VAS and postoperative morphine consumption.[11]

More recent formulations of NSAIDs include an intranasal (IN) ketorolac spray, IV ibuprofen, and topical diclofenac. Southworth and colleagues conducted a randomized, double-blind trial of varying dosages of IV ibuprofen (Caldolor®) versus placebo in 406 patients having an elective abdominal or orthopedic surgery.[12] Those receiving ibuprofen 800 mg every 6 hours consumed 22 % less morphine postoperatively. IV ibuprofen 400 mg every 6 hours appeared to attenuate postoperative pain for up to 24 hours, but had no benefit thereafter when compared to placebo. Aside from dizziness, IV ibuprofen was generally well-tolerated.

In a randomized, double-blind, placebo-controlled study comparing intranasal (IN) ketorolac to placebo in 40 patients undergoing third molar extraction, Grant and Mehlisch demonstrated 31.5 mg IN ketorolac resulted in higher pain relief scores and greater patient satisfaction. 60 % of participants in the study group reported good to excellent pain control compared to 13 % in the placebo group.[13] IN ketorolac 31.5mg every

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

6 hours for 48 hours, then up to four times daily (up to 5 days) in patients undergoing abdominal surgery decreased morphine use over 48 hours and resulted in higher quality of analgesia scores.[14] The authors of this study indicated that pain relief occurred within 20 minutes of administration, which may be due to higher blood brain penetration of ketorolac via the nasal route (cribriform plate). The availability of IN ketorolac can now be used in the ambulatory setting after discharge home taking the same general precautions as IV formulation.

Topical diclofenac exists in several forms, including diclofenac epolamine 1% topical patch (FLECTOR Patch®), diclofenac sodium 1% topical gel (VOLTAREN Gel®), and diclofenac sodium 1.5% w/w liquid (PENNSAID®). A review by Massey and colleagues showed that topical NSAIDs are not only safe, but efficacious in the treatment of acute soft tissue injuries and localized regions of pain.[15] They did find a difference between placebo and topical NSAIDs with regard to local skin irritation but the systemic side effects were less with topical. This research has even led to the National Institute for Health and Clinical Excellence (UK) to recommend topical NSAIDs, along with acetaminophen, as first line treatment for osteoarthritis pain.[16]

A review of diclofenac epolamine topical patch by McCarberg and Argoff discussed the benefits of a patch, as opposed to NSAID gels or creams.[17] These included application of a defined dose of diclofenac, drug delivery over an extended period of time (typically 12 hours), and ease of application. Application of diclofenac sodium 1% gel versus placebo vehicle (identical composition to the gel component of the study drug) applied 4 times daily for 3 months was investigated by Barthel, et al for the treatment of osteoarthritis pain.[18] Results of their study indicated superior analgesia from 1 to 12 weeks and improved function for the same duration. With regards to diclofenac 1.5 % w/w liquid, it has been shown to be as efficacious to oral diclofenac in treating arthritis pain.[19] Gastrointestinal side effects were significantly less common with local skin reactions being more common. A prospective study by Shainhouse and colleagues established the safety of topical diclofenac 1.5% w/w[20] in a study where 793 subjects was followed for an average of 204 days; 144 subjects were followed for 1 year. Application of the study drug, 40 drops four times daily, resulted in local skin reactions (dry skin, contact dermatitis, or dermatitis with vesciles) in 45.1% of study participants. 24 volunteers indicated a similar overall experience when using diclofenac gel and diclofenac liquid. However, they found the gel to have a less desirable scent, found the consistency to be more greasy and sticky when compared to the diclofenac liquid.[21] When side effects have limited oral NSAID use in a multimodal, it may be that IN, IV, and topical formulations of NSAIDs could prove to be of benefit in the perioperative period and should be considered as tools that are emerging for multimodal analgesia.

ANTICONVULSANTS

The use of adjunct agents to treat pain includes the use of anticonvulsants such as gabapentin and pregabalin. Clarke and colleagues studied the effects of varying doses of gabapentin given pre-operatively and post-operatively in addition to femoral/sciatic nerve blocks and celecoxib in 36 patients undergoing total knee arthroplasty. When administered pre- and post-operatively, gabapentin decreased morphine consumption on post-operative days (POD) 2 – 4 and increased the amount of active knee flexion on POD 2 – 3. This occurred without an increase in side effects.[22] A randomized, double-blind, controlled trial of gabapentin in children undergoing spinal fusion determined that pre- and post-operative gabapentin resulted in decreased morphine consumption and improved pain scores through the early stages of recovery up to POD2.[23] However, this attenuation of opioid use and decreased verbal pain scores was temporary. An evaluation of gabapentin's ability to prevent not only acute, but chronic pain by Sen, et al. revealed that gabapentin 1200 mg administered preoperatively decreased morphine consumption, reduced incisional pain at 1, 3, and 6 months, and improved patient satisfaction compared to placebo.[24] Comparing varying dosages of gabapentin in lumbar laminectomy, Khan et al. concluded the timing of dosing (pre-operative versus post-operative) did not affect analgesic efficacy. Gabapentin administered 900 mg or 1200 mg pre- or post-operatively reduced morphine consumption in the first 24 hours post-op and VAS scores without increase in side effects. [25]

The use of similar anticonvulsant, pregabalin, has gained attention because of more favorable pharmacokinetics which includes improved bioavailability and faster achievement of therapeutic levels. 30 patients undergoing laparoscopic cholecystectomy were randomized to receive pregabalin 150 mg 1 hour pre-operatively or placebo by Agarwal, et al.[26] Fentanyl use and VAS scores were measured up to 24 hours postop. Both VAS scores and narcotic use were significantly lower in patients who had received pregabalin. No significant difference in side effects was noted. Mathiesen and colleagues studied a single pre-operative dose of pregabalin 300 mg versus pregabalin 300 mg + dexamethasone 8 mg in 120 patients undergoing total hip arthroplasty.[27] Although pain scores were unaffected, the two groups receiving pregablin pre-op had significantly less morphine consumption at 24 hours post-op. They did notice that those receiving pregabalin had more sedation. A randomized, placebo-controlled, double-blind trial comparing pregabalin (300mg pre-operatively with a tapering dose post-operatively for 14 days) to placebo in 240 patients undergoing total knee arthroplasty has recently been published.[28] Immediate effects observed were decreased epidural drug consumption and increased sedation and confusion on POD 0 and 1. Long-term outcomes included reduced neuropathic pain at 3 and 6 months. A meta-analysis by Zhang et al. demonstrated that pregabalin administered pre-

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

operative, post-operative or both decreases 24 hour morphine consumption while having no effect on post-op pain scales.[29] Analysis also revealed that pregabalin administration led to lower rates of postoperative nausea and vomiting. It is important to note that this meta-analysis did not include any studies of prolonged (more than 2) doses of pregabalin.

TRPV1 AGONIST: CAPSAICIN

Capsaicin, the active component of chili peppers, selectively stimulates unmyelinated C fiber afferent neurons and causes the release of substance P. Following initial depolarization, continued release of substance P in the presence of capsaicin leads to the depletion of substance P and subsequent decrease in C fiber activation. It is a non-narcotic that acts at TRPV1 receptor as an agoinist peripherally. It does not affect the A-delta and A-alpha fibers. Capsaicin causes calcium dependant desensitization.

An ultra-purified capsaicin (ALGRX 4975, 98% pure) has been investigated in a randomized, double-blind, placebo-controlled study of the analgesic efficacy of a single intra-operative wound instillation of 1000 mcg of capsaicin after open mesh groin hernia repair.[30] The VAS pain scores assessed as area under the curve was significantly lower during the first 3 days postoperatively, but this effect was not observed after 72 hours. The local application of capsaicin during hernia repair does not lead to loss of sensory function in patients[31] and has been demonstrated in animal studies not to cause neurotoxicity.[32] Further clinical trials have been carried out in patients undergoing total knee and hip arthroplasty but the entire data has not been published to date. When capsaicin is used in the perioperative setting, the clinical must administer capsaicin well before the end of anesthesia to allow for resolution of the acute burning sensation that occurs immediately after its application. The prolonged duration of analgesia obtained by capsaicin could be extremely valuable in facilitating earlier rehabilitation after painful orthopedic surgery procedures. In contrast to local anesthetic, capsaicin does not affect the motor or autonomic functions and therefore will not interfere with postoperative rehabilitation. The capsaicin patch (NGX-4010) though used for various neuropathic chronic pain conditions, may be useful in acute pain in a multimodal fashion. This needs further large scale randomized controlled trials.

NMDA RECEPTOR ANTAGONISTS:

NMDA receptor antagonists, including ketamine and memantine, have been studied as adjuncts for acute and chronic pain management. Ketamine has options for routes of administration, including IV or IN. Remérand and colleagues demonstrated that an IV bolus at the beginning of surgery followed by a 24 hour infusion decreased morphine consumption in patients undergoing total hip arthroplasty.[33] More interestingly, patients receiving ketamine decreased the incidence of chronic pain. At 6 months 21% of placebo and 8% of ketamine-receiving patients had persistent pain. Loftus et al. found similar results, albeit in opiate-dependent patients undergoing lumbar spine surgery.[34] A ketamine infusion of10μg/kg/min was started at the beginning of surgery after a bolus of 0.5 mg/kg was administered and terminated at skin closure. Significant results included decreased post-op morphine requirements and lower pain scores at 6 weeks post-op.

Memantine was first synthesized in the 1960s and found to antagonize the NMDA receptor in the 1980's. The major site of action is the blockade of current flow through the NMDA receptor channel. Memantine is completely absorbed from the gastrointestinal tract with maximal plasma concentration occurring between 3-8 hours after oral administration. Food does not influence the bioavailability of memantine. Approximately 80% of the administered dose remains as the parent drug. The mean terminal elimination half-life is 60-100 hrs. The dose should be increased in 5 mg increments to 10 mg/day. The recommended maintenance dose is 10 mg twice daily (20 mg/day). There is not an established dose for the treatment of chronic pain states, but case reports and medication trials have started at 5-10 mg bid with increases at 1 week interval to 30 mg/day have been examined. Ketamine causes memory deficits; reproduces with impressive accuracy the symptoms of schizophrenia; is widely abused; and induces vacuoles in neurons at moderate concentrations and cell death at higher concentrations. Memantine, on the other hand, is well tolerated; although instances of psychotic side effects have been reported, in placebo-controlled clinical studies the incidence of side effects is remarkably low.

Memantine, an orally administered non-competitive NMDA receptor antagonist, may prove to be more useful than ketamine as an analgesia adjunct. In one study, daily doses of memantine 30mg decreased phantom pain by up to 80% at one month following upper extremity amputations (in combination with brachial plexus block.)[35] Unfortunately, in patients who have developed phantom pain the pain relief obtained is temporary. Once chronic pain from surgery is established like phantom limb pain, memantine has not been shown to provide analgesia for these patients.

Magnesium seems to exert its analgesic mechanism via inhibition of calcium influx, antagonism of NMDA receptors and prevention of enhanced ligand-induced NMDA signaling in a state of hypo-magnesemia. In addition magnesium may attenuate central sensitization after peripheral tissue injury or inflammation because of dorsal horn NMDA receptors. Magnesium sulfate is available as a 500 mg/ml preservative-free solution for injection. Magnesium administered intravenously lacks efficacy at 4 g, however, 50 mg administered intrathecally has been demonstrated to be effective.[36] Perioperative IV magnesium sulfate at very high doses has been reported to reduce postoperative morphine consumption but not postoperative pain scores. Recently, a dose finding study for IV magnesium determined that administration of magnesium at 40 mg/kg prior to induction, followed by a 10 mg/kg/hour infusion, resulted in a reduction

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

in perioperative analgesic requirements without any major hemodynamic consequences.[37] Higher infusion doses did not offer any advantage. However, since the magnesium ion poorly crosses the blood brain barrier in humans, it is not clear whether the therapeutic effect is related to NMDA antagonism in the central nervous system or peripheral. This needs to be investigated further.

ALPHA – 2 AGONISTS:

Use of alpha-2 agonists as an analgesia adjunct has gained interest with the clonidine and dexmedetomidine. Central and peripheral stimulation of the alpha-2 receptors is believed to be the basic mechanism behind analgesia. Clonidine's role in neuraxial blockade has been described by a number of studies. Recently, Lena and colleagues compared a clonidine/morphine spinal plus remifentanil infusion to a sufentanil infusion for analgesia in 83 patients undergoing open heart surgery.[38] The clonidine/morphine spinal group had faster times to extubation, lower pain scores post-op, used less PCA morphine, and had improved patient satisfaction.

An infusion of dexmedetomidine, administered prior to induction through wound closure, decreased post-anesthesia care unit (PACU) opioid use in 80 patients undergoing laparoscopic bariatric surgery.[39] In addition to this, nausea and vomiting was decreased, and PACU stay shortened. As presumed higher doses of dexmedetomidine required significantly more rescue doses of phenylephrine intra-op, otherwise there were no differences in side effects compared to placebo. Ramadhyani and colleagues reviewed dexmedetomidine's use in IV regional anesthesia.[40] They concluded that when added to IV regional solutions, dexmedetomidine had the ability to prolong analgesia and extend the duration of motor and sensory blockade.

DUAL ACTING AGENT- TAPENTADOL:

Tapentadol is a novel central acting analgesic with duel mode of action.[41] It has analgesic action via the mu-opioid receptor and norepinephrine reuptake inhibition. Combining both effects in a single molecule eliminates the potential for drug-drug interactions inherent in multiple drug therapy. The analgesic effects of tapentadol are independent of metabolic activation with minimal metabolites. Having limited protein binding, no active metabolites and no significant microsomal enzyme induction or inhibition, tapentadol has a limited potential for drug-drug interactions. The duel mode of analgesia is synergistic as demonstrated by pre-clinical work. The immediate release formulation of tapentadol is FDA approved and has been used in the USA since 2008 with 50, 75 and 100 mg. The drug is a schedule II and as such all precautions that need to be followed for other drugs in this category needs to be followed. The equipotent analgesics dose of 100 mg of tapentadol to oxycodone is 15 mg and needs to be administered 4-6 hours.

This compound though has opioid activity also has activity at the descending pathway and therefore may prove to be a very useful analgesic as more clinical experience is obtained in the postoperative setting. For equipotent doses of narcotics, tapentadol has decreased incidence of nausea and vomiting compared to oxycodone.[42] The concept of obtaining equipotent analgesia with decreased postoperative nausea and vomiting can be of great benefit in treating postoperative pain and earlier discharge with significant cost savings.[43] However, further clinical trials need to be carried to demonstrate this phenomenon.

EMERGING TECHNOLOGIES IN PAIN MANAGEMENT

Transdermal fentanyl: The use of patient-controlled delivery has led to the development of other modalities that allow patient control in the delivery of opioid medications. Transdermal delivery systems such as IONSYS®, allow demand dosing of fentanyl at a predetermined interval. The fentanyl HCl iontophoretic transdermal system (ITS) is a patient-controlled approach to analgesic delivery that may avoid some of the problems associated with IV PCA. Fentanyl ITS is a compact, needleless, self-contained system that is preprogrammed to deliver fentanyl 40 mcg across the skin by means of an imperceptible low-intensity electrical current, a method known as iontophoresis. This needless system is under further research before being released for human use. Inhaled fentanyl has been trialed in pediatric and adult patients. There are investigations into the encapsulated liposomal inhaled fentanyl for acute pain- the advantage of this being that it can provide rapid onset and sustained release.

Long acting local Anesthetics: A new developed liposomal long acting bupivacaine is considered for approval by the FDA. A single injection of the liposomal bupivacaine should last 72 hours and is currently considered for infiltration of the local surgical site. Regional analgesia with this product has yet to be established.

Cannabinoids: These compounds have been shown to potent analgesics in animal models. There have been several clinical trials, most of them demonstrating no significant analgesic effect superior to placebo.[44] In fact some of the trials demonstrated increase in VAS with nabilone (oral synthetic cannabinoid) when used in acute postoperative setting. However, these classes of drugs seem to be promising in chronic pain patients.

CONCLUSION

Acute postoperative pain is a predictable response. Recent research has demonstrated that un-treated acute postoperative pain can lead to chronic persistent pain. It is imperative that the health care provider managing acute postoperative pain understand the various options such as the multimodal analgesia so that acute pain can be treated and to prevent the development of chronic pain from surgery.

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

REFERENCES:

1. Buvanendran A, Kroin JS: Multimodal analgesia for controlling acute postoperative pain. Curr Opin Anesthesiol 2009; 22:588-93.
2. Buvanendran A, Kroin JS, Berger RA et al: Up regulation of prostaglandin E2 and interleukins in the central nervous system and peripheral tissue during and after surgery in humans. Anesthesiology 2006; 104: 403-410
3. Graham GG, Scott KF: Mechanism of action of paracetamol. Am J. Ther 2005; 12: 46-55.
4. Göröcs TS, Lambert M, Rinne T, et al. Efficacy and tolerability of ready-to-use intravenous paracetamol solution as monotherapy or as adjunct analgesic therapy for postoperative pain in patients undergoing elective ambulatory surgery: open, prospective study. International Journal of Clinical Practice 2009; 63: 112–120.
5. Salihoglu Z, Yildirim M, Demiroluk S, et al. Evaluation of intravenous paracetamol administration on postoperative pain and recovery characteristics in patients undergoing laparoscopic cholecystectomy. Surgical Laparoscopy, Endoscopy, and Percutaneous Techniques 2009; 19:321–323.
6. Wininger SJ, Miller H, Minkowitz HS, et al: A randomized, double-blind, placebo-controlled, repeated dose study of two intravenous acetaminophen dosing regimens for the treatment of pain after abdominal laparoscopic surgery. Clin Ther 2010; 32: 2348- 69.
7. Sinatra RS, Jahr JS, Reynolds LW et al: Efficacy and safety of single and repeated administration of 1 gram of intravenous acetaminophen injection (paracetamol) for pain management after major orthopedic surgery. Anesthesiology 2005; 102: 822-831.
8. Ender J, Borger MA, Scholz M, et al. Cardiac surgery fast-track treatment in a post-anesthetic care unit: six-month results of the Leipzig fast-track concept. Anesthesiology 2008; 109(1): 61-66.
9. Hong JY, Won Han S, Kim WO, Kil HK. Fentanyl sparing effects of combined ketorolac and acetaminophen for outpatient inguinal hernia repair in children. Journal of Urology 2010; 183:1551–1555.
10. Ong CK, Seymour RA, Lirk P, Merry AF. Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. Anesthesia & Analgesia 2010; 110:1170–1179.
11. Sun T, Sacan O, White PF, et al. Perioperative vs postoperative celecoxib on patient outcome after major plastic surgery procedures. Anesthesia & Analgesia 2008; 106:950-958.
12. Southworth S, Peters J, Rock A, et al. A multicenter, randomized, double-blind, placebo-controlled trial of intravenous ibuprofen 400 and 800 mg every 6 hours in the management of postoperative pain. Clinical Therapeutics 2009; 31(9):1922-1935.
13. Grant GM, Mehlisch DR. Intranasal ketorolac for pain secondary to third molar impaction surgery: a randomized, double-blind, placebo-controlled trial. Journal of Oral and Maxillofacial Surgery 2010; 68:1025–1031.
14. Singla N, Fingla S, Minkowitz HS, et al. Intranasal ketorolac for acute postoperative pain. Current Medical Research and Opinion 2010; 26(8): 1915-23.
15. Massey T, Derry S, Moore RA, et al. Topical NSAIDs for acute pain in adults. Cochrane Database of Systemic Reviews 2010; 16(6): 1-95.
16. National Institute for Health and Clinical Excellence. Osteoarthritis: the care and management of osteoarthritis in adults. NICE clinical guideline 59. http://www.nice.org.uk/nicemedia/pdf/CG59NICEguideline.pdf. Accessed March 21, 2011.
17. McCarberg BH and Argoff CE. Topical diclofenac epolamine patch 1.3% for treatment of acute pain caused by soft tissue injury. International Journal of Clinical Practice 2010; 64(11): 1546-1553.
18. Barthel HR, Haselwood D, Longley III S, et al. Randomized controlled trial of diclofenac sodium gel in knee osteoarthritis. Seminars in Arthritis and Rheumatism 2009; 39(3): 203-212.
19. Moen MD. Topical diclofenac solution. Drugs 2009; 69(18): 2321-2632.
20. Shainhouse JZ, Grierson LM, and Naseer Z. A long-term, open-label study to confirm the safety of topical diclofenac solution containing dimethyl sulfoxide in the treatment of the osteoarthritic knee. American Journal of Therapeutics 2010; 17: 566-5763.
21. Galer BS. A comparative subjective assessment study of PENNSAID and Voltaren Gel, two topical formulations of diclofenac sodium. Pain Practice 2010; 20: 1-9.
22. Clarke H, Pereira S, Kennedy D, et al. Gabapentin decreases morphine consumption and improves functional recovery following total knee arthroplasty. Pain Research & Management 2009; 14:217–222.
23. Rusy L, Hainsworth K, Nelson T, et al. Gabapentin use in pediatric spinal fusion patients: a randomized, double-blind, controlled trial. Anesth Analg 2010; 110:1393–1398.
24. Sen H, Sizlan A, Yanarates O, et al. A comparison of gabapentin and ketamine in acute and chronic pain after hysterectomy. Anesthesia & Analgesia 2009; 109:1645–1650.
25. Khan ZH, Rahimi M, Makarem, et al. Optimal dose of pre-incision/post-incision gabapentin for pain relief following lumbar laminectomy: a randomized study. Acta Anaesthesiologica Scandinacica 2011; 55:306-312.
26. Agarwal A, Gautam S, Gupta D, et al. Evaluation of a single preoperative dose of pregabalin for attenuation of postoperative pain after laparoscopic cholecystectomy. British Journal Anaesthesia 2008; 101:700–704.
27. Mathiesen O, Jacobsen LS, Holm HE, et al. Pregabalin and dexamethasone for postoperative pain control: a randomized controlled study in hip arthroplasty. Br J Anaesth 2008; 101:535–541.
28. Buvanendran A, Kroin JS, Della Valle CJ, et al. Perioperative oral pregabalin reduces chronic pain after total knee arthroplasty: a prospective, randomized, controlled trial. Anesthesia & Analgesia 2010; 110:199–207.
29. Zhang J, Ho KY, Wang Y. Efficacy of pregabalin in acute postoperative pain: a meta-analysis. British Journal of Anaesthesia 2011; Feb 26: 1-9.
30. Aasvang EK, Hansen JB, Malmstrom J, et al. The effect of wound instillation of a novel purified capsaicin formulation on postherniotomy pain: a double-blind, randomized, placebo-controlled study. Anesth Analg 2008; 107:282-291.
31. Aasvang EK, Hansen JB, Kehlet H: Late sensory function after intraoperative capsaicin wound instillation. Acta Anaesthesiol Scand 2010; 54: 224-31.
32. Kissin I: Vanilloid-induced conduction analgesia: selective, dose-dependent, long lasting, with low level of potential neurotoxicity. Anesth Analg 2008; 107: 271-281.
33. Remerand F, Tendre CL, Baud A, et al. The early and delayed analgesic effects of ketamine after total hip arthroplasty: a prospective, randomized, controlled, double-blind study. Anesth Analg 2009; 109(6): 1963-1971.
34. Loftus RW, Yeager MP, Clark JA, et al. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. Anesthesiology. 2010; 113(3):639-646.
35. Schley M, Topfner S, Wiech K, et al. Continuous brachial plexus blockade in combination with the NMDA receptor antagonist memantine prevents phantom pain in acute traumatic upper limb amputees. European J of Pain 2007; 11: 299-308.
36. Buvanendran A, McCarthy RJ, Kroin JS, et al. Intrathecal magnesium prolongs fentanyl analgesia: a prospective, randomized, controlled trial. Anesth Analg. 2002;95:661-666
37. Koinig H, Wallner T, Marhofer P, et al. Magnesium sulfate reduces intra- and postoperative analgesic requirements. Anesth Analg. 1998; 87:206-210
38. Lena P, Balarac N, Lena D et al: Fast track anesthesia with remifentanil and spinal analgesia for cardiac surgery: the effect on pain control and quality of recovery. Journal of Cardiothoracic and Vascular Anesthesia 2008; 22: 536-542.
39. Tufanogullari B, White PF, Peixoto MP et al: Dexmedetomidine infusion during laparoscopic bariatric surgery: the effect on recovery outcome variables. Anesth Analg 2008; 106: 1741-1748.
40. Ramadhyani U, Park JL, Carollo DS et al: Dexmedetomidine: clinical application as an adjuct for intravenous regional anesthesia. Anesthesiology clinics 2010; 28: 709-722.
41. Afilalo M, Stegmann JU, Upmalis D et al: Tapentadol immediate release: a new treatment option for acute pain management. J Pain Res 2010; 8: 1-9
42. Etropolski M, Kelly K, Okamoto A, Rauschkolb C: Comparable efficacy and superior gastrointestinal tolerability (nausea, vomiting, constipation) of tapentadol compared with oxycodone hydrochloride. Adv Ther 2011; April. (not yet in print)
43. Kwong WJ, Ozer-Stillman I, Miller JD et al: Cost-effectiveness analysis of tapentadol immediate release for the treatment of acute pain. Clin Ther 2010; 32: 1768-81.
44. Beaulieu P: Effects of nabilone, a synthetic cannabinoid, on postoperative pain. Can J Anaesth 2006; 53: 769-75.

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

You Can't Put It Back: Anesthetic Management for Lung Resection

Peter D. Slinger, MD, FRCPC
Professor of Anesthesia,
University of Toronto,
Canada

This review will focus on patients for pulmonary resection surgery but the general principles apply to patients with pulmonary disease having any intra-thoracic surgical procedure. An evidence-based strategy will be developed to allow the Anesthesiologist to stratify patients according to their risk of perioperative complications and also to direct anesthetic management to modify the risk. To assess the patients preoperatively it is necessary to have an understanding of the risks specific to this type of surgery.[1] The major cause of perioperative morbidity and mortality in the thoracic surgical population is respiratory complications. For other types of surgery, cardiac and vascular complications are the leading cause of early perioperative morbidity and mortality.

The best assessment of respiratory function comes from a history of the patient's quality of life.[2] It is useful to have objective measures of pulmonary function that can be used to guide anesthetic management and to have this information in a format that can be easily transmitted between members of the health care team. There are many factors that determine overall respiratory performance.[3] It is useful to think of the respiratory function in three related but somewhat independent areas: respiratory mechanics, gas exchange, and cardio-respiratory interaction.

1) Respiratory Mechanics: Many tests of respiratory mechanics and volumes show correlation with post-thoracotomy outcome. It is useful to express these as a percent of predicted volumes corrected for age, sex and height (e.g.: FEV1 %). Of these, the most valid single test for post-thoracotomy respiratory complications is the predicted postoperative forced expiratory volume in one second (ppoFEV1 %) calculated as:[4]

ppoFEV1 % = preoperative FEV 1% x (1- % functional lung tissue removed/100).

A study from the 1980's found that patients with a ppoFEV1 >40% had no or minor post-resection respiratory complications. Major respiratory complications were only seen in the subgroup with ppoFEV1 <40% and patients with ppoFEV1 <30% required postoperative mechanical ventilatory support.[5] The use of epidural analgesia has decreased the incidence of complications in the high-risk group.[6]

2) **Lung Parenchymal Function:** Arterial blood gas data such as PaO_2 < 60 mmHg or $PaCO_2$ > 45 mmHg have been used as cut-off values for pulmonary resection. Cancer resections have now been successfully done or even combined with volume reduction in patients who do not meet these criteria.[7] The most useful test of the gas exchange capacity of the lung is the diffusing capacity for carbon monoxide (DLCO).[8] The DLCO correlates with the total functioning surface area of alveolar-capillary interface. The DLCO can be used to calculate a post-resection (ppo) value using the same calculation as for the FEV1. A ppoDLCO <40% predicted correlates with both increased respiratory and cardiac complications and is relatively independent of the FEV1.[9]

3) **Cardio-pulmonary Interaction:** The most important assessment of respiratory function is an assessment of the cardio-pulmonary interaction. The traditional test is stair climbing.[10] The ability to climb 3 flights or more is closely associated with decreased mortality and morbidity. Less than 2 flights is very high risk. Formal laboratory exercise testing with maximal oxygen consumption (VO_2max) is the "gold standard" for assessment of cardio-pulmonary function. Climbing 5 flights of stairs approximates a VO_2 max of >20ml/kg/min and less than one flight a VO_2 max <10ml/kg/min.[11] In a high-risk group of patients (mean pre-operative FEV1= 41% predicted) there was no perioperative mortality if the preoperative VO_2max was >15ml/kg/min.[12] Alternatives to VO_2max include the six-minute walk test (6MWT)[13] and exercise oximetry.[14] For patients with moderate to severe COPD the 6MWT has a high correlation with VO_2max, which can be estimated from the distance in meters/30 (i.e. for a 6MWT distance of 450m, VO_2max = 450/30= 15 ml/kg/min).[15]

4) **Ventilation Perfusion (V/Q) scintigraphy:** Prediction of post-resection pulmonary function can be further refined by assessment of the pre-operative contribution of the lung or lobe to be resected using V/Q lung scanning.[16] If the lung region to be resected is non- or minimally functioning the prediction of post-operative function can be modified accordingly. This is particularly useful in pneumonectomy patients and should be considered for any patient who has a ppoFEV1 <40%. Other tests of pulmonary function such as split-lung function studies and flow-volume loops have not shown sufficient predictive validity for widespread universal adoption in potential lung resection patients.

5) **Combination of Tests:** No single test of respiratory function has shown adequate validity as a sole pre-operative assessment. Prior to surgery an estimate of respiratory function in all 3 areas: lung mechanics, parenchymal function and cardio-pulmonary interaction should be made for each patient. If a patient has a ppoFEV1 >40% it should be possible for that patient to be extubated in the operating room at the conclusion of surgery assuming the patient is

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

alert, warm and comfortable ("AWaC"). If the ppoFEV1 is >30% and exercise tolerance and lung parenchymal function exceed the increased risk thresholds then extubation in the operating room may be possible depending on the status of associated diseases (see below). Those patients in this subgroup who do not meet the minimal criteria for cardio-pulmonary and parenchymal function should be considered for staged weaning from mechanical ventilation post-operatively so that the effect of the increased oxygen consumption of spontaneous ventilation can be assessed. Patients with a ppoFEV1 20-30% and favorable predicted cardio-respiratory and parenchymal function can be considered for early extubation if thoracic epidural analgesia if used. The validity of this approach has been confirmed by the National Emphysema Treatment Trial which found an unacceptably high mortality for lung volume reduction surgery in patients with preoperative FEV1 and DL_{CO} values <20% predicted.[17]

INTER-CURRENT MEDICAL CONDITIONS:

1) **Reactive Airways Disease:** Broncho-constriction is assessed by history, physical examination and evaluation of pulmonary function response to bronchodilators. All COPD patients should receive maximal bronchodilator therapy as guided by their symptoms. In a patient who is poorly controlled on sympathomimetic and anticholinergic bronchodilators, a trial of corticosteroids may be beneficial.[18] It is not clear if corticosteroids are as beneficial in COPD as they are in asthma.

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

With advances in Anesthetic management the incidence of life-threatening intra-operative bronchospasm has become very low.[19] However, the Anesthesiologist must always respect the management principles for patients with reactive airways: preoperative optimization of bronchodilation, minimal (or no) instrumentation of the airways, instrument the airways only after appropriate depth of anesthesia with a bronchodilating anesthetic (Propofol, Ketamine, Sevoflurane), and maintenance of anesthesia with a bronchodilating anesthetic and appropriate warming and humidification of inspired gases.[20] In patients with bronchial hyper-reactivity (FEV1 <70% and >10% increase with bronchodilator) on regular bronchodilator therapy, post-intubation wheezing can be significantly reduced by addition of a 5-day preoperative course of corticosteroids (methylprednisolone 40mg/day p.o.).[21]

2) **Age:** If a patient is 80 years of age and has a stage I lung cancer, their chances of survival to age 85 are better with the tumor resected than without.[22] However, the rate of respiratory complications (40%) is double that expected in a younger population and the rate of cardiac complications (40%), particularly arrhythmias, triple that which should be seen in younger patients. Although the mortality from lobectomy in the elderly is acceptable, the mortality from pneumonectomy (22% in patients >70 years),[23] particularly right pneumonectomy, is excessive. Pulmonary resection in the elderly should be regarded as a high-risk procedure for cardiac complications and cardiopulmonary reserve is the most important predictor of outcome in this population.[24]

3) **Cardiac Disease:** Cardiac complications are the second most common cause of peri-operative morbidity and mortality in the thoracic surgical population.

a) Ischemia. the majority of pulmonary resection patients have a smoking history and already have one risk factor for coronary artery disease.[25] Pulmonary resection surgery is an "intermediate risk" procedure in terms of peri-operative cardiac ischemia.[26] Non-invasive testing is indicated in patients with major (unstable ischemia, recent infarction, severe valvular disease, significant arrhythmia) or intermediate (stable angina, remote infarction, previous congestive failure, or diabetes) clinical predictors of myocardial risk and also in the elderly.

b) Arrhythmia: Dysrhythmias, particularly atrial fibrillation, are a frequent complication of pulmonary resection surgery.[27] Factors known to correlate with an increased incidence of arrhythmia are the amount of lung tissue resected, age, intraoperative blood loss, and intra-pericardial dissection.[28] Prophylactic therapy with Digoxin has not been shown to prevent these arrhythmia's. Diltiazem has been shown to be effective.[29]

4) **Renal Dysfunction.** Renal dysfunction following pulmonary resection surgery is associated with a very high incidence of mortality (19%).[30] The factors which are associated with an elevated risk of renal impairment are: history of previous renal dysfunction, diuretic therapy, pneumonectomy, postoperative infection and transfusion.

Physiotherapy: Patients with COPD have fewer post-operative pulmonary complications when a program of chest physiotherapy is initiated preoperatively.[31] Among COPD patients, those with excessive sputum benefit the most from chest physiotherapy.[32] A comprehensive program of pulmonary rehabilitation involving physiotherapy, exercise, nutrition and education has been shown to consistently improve functional capacity for patients with severe COPD.[33] Atelectasis in the post-operative period leads to increased capillary permeability and an inflammatory response with subsequent lung injury

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

if it persists[34] it should be treated with aggressive physiotherapy.[35]

Lung Cancer: At the time of initial assessment cancer patients should be assessed for the "4-M's" associated with malignancy: mass effects,[36] metabolic abnormalities, metastases[37] and medications. The prior use of medications which can exacerbate oxygen induced pulmonary toxicity such as bleomycin should be considered.[38] Recently we have seen several lung cancer patients who received preoperative chemotherapy with cis-platinum and then developed an elevation of serum creatinine when they received non-steroidal anti-inflammatory analgesics (NSAIDS) post-operatively. For this reason we now do not routinely administer NSAIDS to patients who have been treated recently with cis-platinum.

Smoking Cessation: In non-pulmonary surgery a pre-operative smoking cessation program can significantly decrease the incidence of respiratory complications (8 weeks abstinence), wound complications (4 weeks abstinence) and intra-operative myocardial ischemia (48 hr. abstinence).[39] However in thoracic surgical patients, pulmonary complications are decreased in those who are not smoking versus those who continue to smoke up until the time of surgery.[40] The perioperative period is a specific stimulus for patients to stop smoking, 55% patients were found to remain abstinent from smoking one-year after aorto-coronary bypass, versus only 25% 1 year after angioplasty and 14% after angiography and physician counseling is a major part of the stimulus[41]. Smoking cessation can be achieved in >50% of perioperative patients with a structured program and can result in an overall decrease of complications of >50%.[42]

Perioperative Surgical Environment Factors: There are multiple factors in the surgical environment that can contribute to lung injury in this patient. One of the most obvious is the surgical approach. If these procedures can be done with a minimally invasive technique vs. an open laparotomy the decrease in respiratory complications is well documented.[43]

Atelectasis: Atelectasis is a frequent post-operative complication of open surgical procedures. Atelectasis occurs intra-operatively as part of essentially any general anesthetic.[44] Anesthesiologists are aware of this and techniques to avoid it with use of air oxygen mixtures, PEEP and recruitment maneuvers are used frequently.[45] However, Anesthesiologists are often not aware that atelectasis is a pathological state, and in the post-operative period leads to increased capillary permeability and an inflammatory response with subsequent lung injury if it persists.[46] Both retrospective[47] and prospective[48] studies have consistently shown that appropriate thoracic epidural analgesia reduces the incidence of respiratory complications (atelectasis, pneumonia and respiratory failure)after major abdominal and thoracic surgery. It has also been recently demonstrated that aggressive physiotherapy with CPAP in the post-operative period in patients who develop early desaturation after major abdominal surgery leads to lower rates of major respiratory complications.[49]

Postoperative Analgesia: The strategy for postoperative analgesia should be developed and discussed with the patient during the initial preoperative assessment. Only epidural techniques have been shown to consistently decrease post-thoracotomy respiratory complications.[50,51] Thoracic epidural analgesia is superior to lumbar epidural analgesia due to the synergy which local anesthetics have with opioids in producing neuraxial analgesia. Studies suggest that epidural local anesthetics increase segmental bio-availability of opioids in the cerebrospinal fluid[52] and increase the binding of opioids by spinal cord receptors.[53] Only the segmental effects of thoracic epidural local anesthetic and opioid combinations can reliably produce increased analgesia with movement and increased respiratory function following a chest incision.[54] In patients with coronary artery disease, thoracic epidural local anesthetics reduce myocardial oxygen demand and supply in proportion,[55] unlike lumbar epidural local anesthetics.[56] Thoracic epidural analgesia has been shown to be associated with a decreased risk of requiring post-operative ventilatory support.[57]

At the time of initial pre-anesthetic assessment the risks and benefits of the various forms of post-thoracotomy analgesia should be explained to the patient. Potential contraindications to specific methods of analgesia should be determined such as coagulation problems, sepsis or neurologic disorders. When it is not possible to place a thoracic epidural due to concerns with patient consent or other contraindications, our current second choice for analgesia is a paravertebral infusion of local anesthetic via a catheter placed intraoperatively in the open hemithorax by the surgeon.[58] This is combined with intravenous patient-controlled opioid analgesia and NSAIDS.

If the patient is to receive prophylactic anticoagulants and it is elected to use epidural analgesia, appropriate timing of anticoagulant administration and neuraxial catheter placement need to be arranged. ASRA guidelines suggest an interval of 2-4 hours before or one hour after catheter placement for prophylactic heparin administration.[59] Low molecular weight heparin (LMWH) precautions are less clear, an interval of 12-24 hours before and 24 hours after catheter placement are recommended.

SUMMARY

Recent advances in anesthetic care have improved outcomes for patients with respiratory disease having major surgery. Understanding and stratifying the perioperative risks allows the anesthesiologist to develop a systematic focused approach to these patients, which can then be used to both assess and manage these patients.

REFERENCES

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

1. Slinger PD, Johnston MR. Preoperative Assessment: An Anesthesiologist's Perspective. Thorac Surg Clin 2005, 15: 11-25
2. British Thoracic Society. Guidelines on the selection of patients with lung cancer for surgery. Thorax 2001; 56: 89-108
3. Epstein SK, Failing LJ, Daly BDT, Celli BR. Predicting complications after pulmonary resection. Chest 1993;104:694-700.
4. Win T, Jackson A, Sharples L, et al. Relationship between pulmonary function and lung cancer surgical outcome. Eur Respir J 2005, 25: 594-9
5. Nakahara K, Ohno K, Hashimoto J, et al. Prediction of postoperative respiratory failure in patients undergoing lung resection for cancer. Ann Thorac Surg 1988;46: 549-52.
6. Cerfolio RJ, Allen MS, Trastak VF, Deschamps C, Scanbon PD, Pairolero PC. Lung resection in patients with compromised pulmonary function. Ann Thorac Surg 1996;62:348-51.
7. McKenna RJ, Fischel RJ, Brenner M, Gelb AF. Combined operations for lung volume reduction surgery and lung cancer. Chest 1996;110: 885-8.
8. Amar D, Munoz D, Weiji S, et al. A clinical prediction rule for pulmonary complications after thoracic surgery for primary lung cancer. Anesth Analg 2010; 110: 1343-8
9. Wang J, Olak J, Ferguson MK. Diffusing capacity predicts mortality but not long-term survival after resection for lung cancer. J Thorac Cardiovasc Surg 1999; 17: 581-85.
10. Olsen GN, Bolton JWR, Weiman DS, Horning CA. Stair climbing as an exercise test to predict postoperative complications of lung resection. Chest 99: 587-90, 1991
11. Beckles MA, Spiro SG, Colice GL, et al. The physiologic evaluation of patients with lung cancer being considered for resectinal surgery. Chest 2003; 123: 105s-114s
12. Walsh GL, Morice RC, Putnam JB, et al. Resection of lung cancer is justified in high risk patients selected by oxygen consumption. Ann Thorac Surg 1994;58:704.
13. Cahalin L, Pappagianapoulos P, Prevost S, Wain J, Ginns L. The relationship of the 6-min walk test to maximal oxygen consumption in transplant candidates with end-stage lung disease. Chest 1995;108:452-57.
14. Ninan M, Sommers KE, Landranau RJ, et al. Standardized exercise oximetry predicts post pneumonectomy outcome. Ann Thorac Surg 1997;64:328-33.
15. Carter R, Holiday DB, Stocks J, et al. Predicting oxygen uptake for men and women with moderate to severe chronic obstructive pulmonary disease. Arch Phys Med Rehabil 2003; 84: 1158-64
16. Vesselle H. Functional imaging before pulmonary resection. Semin Thoracic Cardiovasc Surg 2001; 13: 126-135.
17. National Emphysema Treatment Trial Research Group. A Randomized Trial Comparing Lung-Volume-Reduction Surgery with Medical Therapy for Severe Emphysema. New Eng J Med 348: 2059-73, 2003
18. Nisar M, Eoris JE, Pearson MG, Calverly PMA. Acute broncho-dilator trials in chronic obstructive pulmonary disease. Am Rev Resp Dis 1992; 146:555
19. Bishop M, Cheny F. Anesthesia for patients with asthma: low risk but not no risk. Anesthesiology 1996, 85: 455-6
20. Hurford W. The bronchospastic patient. Int Anesthesiol Clinics 2000, 38: 77-90
21. Silvanus MT , Groeben H, Peters J. Corticosteroids and Inhaled Salbutamol in Patients with Reversible Airway Obstruction Markedly Decrease the Incidence of Bronchospasm after Tracheal Intubation. Anesthesiology 2004; 100: 1052-57
22. Osaki T, Shirakusa T, Kodate M, et al. Surgical treatment of lung cancer in the octogenarian. Ann Thorac Surg 1994;57:188-93.
23. Mizushima Y, Noto H, Sugiyama S, et al. Survival and prognosis after pneumonectomy in the elderly. Ann Thorac Surg 1997;64:193-8.
24. Brunelli A, Monteverde M, Al Rafai M , et al. Stair climbing test as a predictor of cardiopulmonary complications after pulmonary lobectomy in the elderly. Ann Thorac Surg 2004; 77: 266-70
25. Barry J, Mead K, Nadel EC, et al. Effect of smoking on the activity of ischemic heart disease. JAMA 1989; 261:398-402.
26. ACC/AHA Guideline Update for Perioperative Cardiovascular Evaluation for Noncardiac Surgery-Executive Summary. Anesth Analg 2002;94:1052-64
27. Ritchie AJ, Danton M, Gibbons JRP. Prophylactic digitalisation in pulmonary surgery. Thorax 1992;47:41-3.
28. Didolkar MS, Moore RH, Taiku J. Evaluation of the risk in pulmonary resection for bronchogenic carcinoma. Am J Surg 1974;127:700-705.
29. Amar D, Roistacher N, Burt ME, et al. Effects of diltiazem versus digoxin on dysrhythmias and cardiac function after pneumonectomy. Ann Thorac Surg 1997;63:1374-81.
30. Golledge J, Goldstraw P. Renal impairment after thoracotomy: incidence, risk factors and significance. Ann Thorac Surg 1994;58:524-8.
31. Warner DO. Preventing postoperative pulmonary complications. Anesthesiology 2000;92:1467-71.
32. Selsby D, Jones JG. Some physiological and clinical aspects of chest physiotherapy. Br J Anaesth 1990;64:621-31.
33. Kesten S. Pulmonary Rehabilitation and Surgery for end-stage lung disease. Clinic Chest Med. 1997;18:174-81.
34. Duggan M, Kavanagh B. Pulmonary Atelectasis a pathological perioperative entity. Anesthesiology 2005; 102: 838-54
35. quadrone V, Coha M, Cerutti E, et al. Continuous positive airway pressure for treatment of Postoperative hypoxemia. JAMA 2005; 293: 589-95
36. Gilron I, Scott WAC, Slinger P, Wilson JAS. Contralateral lung soiling following laser resection of a bronchial tumor. J Cardiothorac Vasc Anesth 1994;8:567-9.
37. Mueurs MF. Preoperative screening for metastases in lung cancer patients. Thorax 1994;49:1-3.
38. Ingrassia TS III, Ryu JH, Trasek VF, Rosenow EC III. Oxygen-exacerbated bleomycin pulmonary toxicity. Mayo Clin Proc 1991;66:173-8.
39. Warner DO. Helping surgical patients quit smoking: why, when and how. Anesth Analg 2005; 101: 481-7
40. Bonde P, McManus K, McAnespie M, McGuigan J. Lung surgery: identifying the subgroup at risk for sputum retention. Eur J Cardiothorac Surg 2002;22:18-22.
41. Crouse JR, Hagaman AP. Smoking cessation in relation to cardiac procedures. Am J Epidemiol 1991; 134: 699-703
42. Thomsen T, Tonnesen H, Moller AM. Effect of preoperative smoking cessation interventions on postoperative complications and smoking cessation. Br J Surg 2009; 96: 451-61
43. Ramivohan SM, Kaman L, Jindal R, et al. Postoperative pulmonary function in laparoscopic versus open cholecystectomy: prospective, comparative study. Indian J Gastroenerol 2005; 24: 6-8
44. Lindberg P, Gunnarsson L, Tokics L, et al. Atelectasis and lung function in the postoperative period. Acta Anaesthesiol Scand 1992, 36 : 546-53
45. Tusman G. Bohm SH. Suarez-Sipmann F Alveolar recruitment improves ventilatory efficiency of the lungs during anesthesia. Can J Anesth 2004: 51: 723-7
46. Duggan M, Kavanagh B. Pulmonary Atelectasis a pathological perioperative entity. Anesthesiology 2005; 102: 838-54
47. Ballantyne,J.C.; Carr,D.B.; deFerranti,S. The comparative effects of postoperative analgesic therapies on pulmonary outcome: cumulative meta-analysis of randomized, controlled trials. Anesth Analg 1998; 86: 598-612
48. Rigg J, Jamrozik K, Myles P, et al. Epidural anaesthesia and analgesia and outcome of major surgery: a randomized trial. Lancet 2002, 359: 1276-82
49. Squadrone V, Coha M, Cerutti E, et al. Continuous positive airway pressure for treatment of Postoperative hypoxemia. JAMA 2005; 293: 589-95
50. Rigg J, Jamrozik K, Myles P, et al. Epidural anaesthesia and analgesia and outcome of major surgery: a randomized trial. Lancet 2002, 359: 1276-82
51. Licker M, de Perrot M, Hohn L, et al. Perioperative mortality and major cardio-pulmonary complications after lung surgery for non-small call carcinoma. Eur J Cardiothorac Surg 1999;15: 314-9.
52. Hansdottir V, Woestenborghs R, Nordberg G. The pharmacokinetics of continuous epidural sufentanil and bupivacaine infusion after thoracotomy. Anesth Analg 1996;83:401-6.
53. Tejwani GA, Rattan AK, Mcdonald JS. Role of spinal opioid receptors in the antinociceptive interactions between intrathecal morphine and bupivacaine. Anesth Analg 1992;74:726-34.
54. Hansdottir V, Bake B, Nordberg G. The analgesic efficiency and adverse effects of continuous epidural sufentanil and bupivacaine infusion after thoracotomy. Anesth Analg 1996;83:394-400.
55. Saada M, Catoire P, Bonnet F,et al. Effect of thoracic epidural anesthesia combined with general anesthesia on segmental wall motion assessed by transesophageal echocardiography. Anesth.Analg 1992;75:329-335.
56. Saada M, Duval A-M, Bonnet F, et al. Abnormalities in myocardial wall motion during lumbar epidural anesthesia. Anesth Analg 1989;71: 26-33.
57. Cywinski JB, Xu M, Sessler D, et al. Predictors of prolonged post-operative endotracheal intubation in patients undergoing thoracotomy for lung resection. J Cardiothorac Vasc Anesth 2009; 23: 766-9
58. Karmakar MK. Thoracic paravertebral block. Anesthesiology 2001;95:771-80.
59. Horlocker TT, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy. ASRA Guidelines. Reg Anesth Pain Med 2010; 35: 64-101.

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

Does Blood Save Lives?

Colleen Koch, MD, MS, MBA
Professor of Anesthesiology, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Vice Chair, Research and Education, Department of Cardiothoracic Anesthesia Cleveland Clinic
Cleveland, Ohio

OBJECTIVES

The objective of this session is for the participant to recognize the association between red cell transfusion and adverse outcomes in patients with cardiovascular disease undergoing cardiac surgery. In addition, the participant will become aware of structural and functional changes in red cell products with increasing storage duration and implications of these changes on patient outcome.

While life saving, red cell transfusion has been associated with increased morbidity, higher in-hospital mortality and reduced long- term survival in patients undergoing surgery. [1,2,3] A higher prevalence of cardiac, neurologic and pulmonary morbidities have been reported for patients transfused in the perioperative period. Transfusion of RBC has also been attributed to more infectious complications such as pneumonia, septicemia and bacteremia and deep and superficial wound infections compared to those not receiving a red cell transfusion.[4,5] A recent investigation of patients undergoing elective major vascular surgery noted that perioperative transfusion in patients who were not anemic and who were clinically stable were at significant risk for myocardial infarction and death.[6] An investigation examining the role of transfusion in perioperative lung injury reported more pulmonary complications in patients transfused red cells and fresh frozen plasma. Pulmonary complications included respiratory distress, longer intubation times, and reintubation for pulmonary reasons. Interestingly, a majority of patients both transfused and not transfused had lung injury following cardiopulmonary bypass manifested by a PaO_2/FiO_2 ratio less than 300. Differentiation of transfusion associated circulatory overload, and transfusion related lung injury is particularly problematic in this patient population.[7] Excess morbidity associated with transfusion often translates to longer intensive care unit and hospital length of stay.

There are a number of structural and functional changes that occur with red cell storage that may in part be related to a number of adverse outcomes associated with transfusion. Following donation blood is routinely stored for up to 42 days. The influence of prolonged storage on impairment of oxygen delivery and clinical outcomes is controversial. An analysis of changes occurring during red cell storage suggests that storage induced defects in RBC units could be related to transfusion associated adverse outcomes. The authors noted RBC deformability gradually decreased with increasing storage duration in addition to decreases in 2, 3 DPG, and increases in potassium, lactate, and free hemoglobin with increasing duration of storage.[8] Reynolds et al reported that loss of nitric oxide bioactivity with routine blood storage adversely impacted red blood cell hypoxic vasodilatory activity with associated impairment in blood flow. Interestingly, they reported that repletion of nitric oxide bioactivity could restore red blood cell vasodilatory activity and improve tissue blood flow.[9] A recent laboratory investigation by Sweeney et al commented on a mechanism whereby stored red blood cells could contribute to excess thrombotic complications. In their investigation red cell storage age had a significant impact on thrombin generation. The authors noted that some stored red blood cells released microvesicles which expressed phosphatidylserine and were capable of facilitating thrombin generation.[10] Relevy and colleagues suggested the potential risk with transfusion may be related to impaired red blood cell rheology. The authors examined the effect of cold storage on RBC adherence and deformability noting that red blood cell flow properties were affected by cold storage. Cold storage increased the number of adherent red blood cells and strength of their interaction with endothelial cells. A marked decrease in RBC deformability was reported as early as 2 weeks into the storage period.[11] In a laboratory investigation Rigamonti et al demonstrated that red cell storage limits the ability of red blood cells to deliver oxygen to brain tissue. They noted fresh blood demonstrated greater increases in regional cerebral blood flow and tissue oxygen tension compared to stored blood.[12]

There are a number of clinical investigations that report an increase risk for adverse outcomes associated with storage duration. In cardiac surgery, administration of red cells older than 14 days storage duration was associated with reduced survival and an increase in complications following surgery.[13,14] In trauma patients, Zallen et al reported a risk adjusted increase in multisystem organ failure with increasing number of RBC transfused and with red cell units of older storage duration, beyond 14 and 21 days storage.[14] Leal-Noval et al examined transfusion on cerebral oxygenation in patients with traumatic brain injury. Younger blood stored less than 19 days storage duration was associated with improved cerebral oxygenation versus older blood.[15] In a separate investigation Leal-Noval S et al suggested storage duration longer than 28 days may be a risk factor for nosocomial pneumonia.[16] Of note, there are investigations that do not find an association between prolonged red cell storage and adverse outcomes.[17,18]

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited

While transfusion is necessary for some patients, it has a strong reported association with adverse morbid outcomes. Whether morbidity is due intrinsic properties of allogenic red cells or to the biochemical and mechanical properties that occur with increasing storage duration is unsettled. Furthermore, the optimal hematocrit to initiate a transfusion in an individual patient is unknown in part because of our inability to measure tissue oxygenation at the bedside.

REFERENCES

1. Koch CG, Li L, Duncan AI, et al. Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. Crit Care Med. Jun 2006;34(6):1608-1616.
2. Koch CG, Li L, Duncan AI, et al. Transfusion in coronary artery bypass grafting is associated with reduced long-term survival. Ann Thorac Surg. May 2006;81(5):1650-1657.
3. Kuduvalli M, Oo AY, Newall N, et al. Effect of peri-operative red blood cell transfusion on 30-day and 1-year mortality following coronary artery bypass surgery. Eur J Cardiothorac Surg. Apr 2005;27(4):592-598.
4. Banbury MK, Brizzio ME, Rajeswaran J, Lytle BW, Blackstone EH. Transfusion increases the risk of postoperative infection after cardiovascular surgery. J Am Coll Surg. Jan 2006;202(1):131-138.
5. Rogers MA, Blumberg N, Saint S, Langa KM, Nallamothu BK. Hospital variation in transfusion and infection after cardiac surgery: a cohort study. BMC Med. 2009;7:37.
6. Bursi F, Barbieri A, Politi L, et al. Perioperative red blood cell transfusion and outcome in stable patients after elective major vascular surgery. Eur J Vasc Endovasc Surg. Mar 2009;37(3):311-318.
7. Koch C, Li L, Figueroa P, Mihaljevic T, Svensson L, Blackstone EH. Transfusion and pulmonary morbidity after cardiac surgery. Ann Thorac Surg. Nov 2009;88(5):1410-1418.
8. Bennett-Guerrero E, Veldman TH, Doctor A, et al. Evolution of adverse changes in stored RBCs. Proc Natl Acad Sci U S A. Oct 23 2007;104(43):17063-17068.
9. Reynolds JD, Ahearn GS, Angelo M, Zhang J, Cobb F, Stamler JS. S-nitrosohemoglobin deficiency: a mechanism for loss of physiological activity in banked blood. Proc Natl Acad Sci U S A. Oct 23 2007;104(43):17058-17062.
10. Sweeney J, Kouttab N, Kurtis J. Stored red blood cell supernatant facilitates thrombin generation. Transfusion. Apr 29 2009.
11. Relevy H, Koshkaryev A, Manny N, Yedgar S, Barshtein G. Blood banking-induced alteration of red blood cell flow properties. Transfusion. Jan 2008;48(1):136-146.
12. Rigamonti A, McLaren AT, Mazer CD, et al. Storage of strain-specific rat blood limits cerebral tissue oxygen delivery during acute fluid resuscitation. Br J Anaesth. Mar 2008;100(3):357-364.
13. Koch CG, Li L, Sessler DI, et al. Duration of red-cell storage and complications after cardiac surgery. N Engl J Med. Mar 20 2008;358(12):1229-1239.
14. Zallen G, Offner PJ, Moore EE, et al. Age of transfused blood is an independent risk factor for postinjury multiple organ failure. Am J Surg. Dec 1999;178(6):570-572.
15. Leal-Noval SR, Marquez-Vacaro JA, Garcia-Curiel A, et al. Nosocomial pneumonia in patients undergoing heart surgery. Crit Care Med. Apr 2000;28(4):935-940.
16. Leal-Noval SR, Jara-Lopez I, Garcia-Garmendia JL, et al. Influence of erythrocyte concentrate storage time on postsurgical morbidity in cardiac surgery patients. Anesthesiology. Apr 2003;98(4):815-822.
17. van de Watering L, Lorinser J, Versteegh M, Westendord R, Brand A. Effects of storage time of red blood cell transfusions on the prognosis of coronary artery bypass graft patients. Transfusion. Oct 2006;46(10):1712-1718.
18. Yap CH, Lau L, Krishnaswamy M, Gaskell M, Yii M. Age of transfused red cells and early outcomes after cardiac surgery. Ann Thorac Surg. Aug 2008;86(2):554-559.

©2011 International Anesthesia Research Society. Unauthorized Use Prohibited