

CLINICAL LEARNING GUIDES

**CASE-BASED ANESTHESIA**



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## **GEORGE SHORTEN**

Professor of Anaesthesia and Intensive Care Medicine  
Department of Anaesthesia  
University College of Cork  
Consultant Anaesthetist  
Department of Anaesthesia  
Cork University Hospital  
Cork, Ireland

## **STEPHEN F. DIERDORF, MD**

Professor and Vice Chairman  
Department of Anesthesia  
Indiana University School of Medicine  
Indianapolis, Indiana

## **GABRIELLA IOHOM, MD, PhD**

Consultant Anaesthetist/Senior Lecturer  
Cork University Hospital  
University College Cork  
Cork, Ireland

## **CHRISTOPHER J. O'CONNOR, MD**

Professor of Anesthesiology  
Rush University Medical Center  
Chicago, Illinois

## **CHARLES W. HOGUE, JR., MD**

Associate Professor  
Department of Anesthesiology and Critical Care Medicine  
The Johns Hopkins Medical Institutions and The Johns Hopkins Hospital  
Baltimore, Maryland



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*Dedicated to the memory of Gerard McDonnell.*

*Dr. Shorten wishes to thank Ms. Renee Mooney  
for her incomparable efficiency and hard work.*

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# FOREWORD

The discovery and application of anesthesia is the most important contribution of American medicine to mankind. Its impact exceeds even the elucidation of the human genome. Without visionary discoveries by pioneers in anesthesiology, the explosive growth in type, complexity, and safety of surgical procedures would not have occurred. More importantly, anesthesiology is considered to be the lead specialty in patient safety.

The core principle that drives these advances is training and continuing education. It is interesting to note that, in the 19th century, anesthesiology was considered a “technique” with little scientific merit. It was not until 100 years later that the specialty developed a rigorous scientific foundation with postgraduate training programs. Even more astounding is the fact that, into the late 20th century, there was a paucity of books authored by North Americans. Textbooks supporting resident education, preparation for board examinations, and reference for clinical care were predominantly British in origin.

In the 1980s the educational scene changed dramatically. Residents and fellows were recruited from the upper tier of medical school graduates. In addition to publication of core and specialty textbooks and journals, application of electronic media, such as the Internet, has revolutionized the specialty of anesthesiology. The American Board of Anesthesiology has stated, “The ability to independently acquire and process information in a timely manner is central to assure individual responsibility for all aspects of patient care.” Although use of the Internet and other electronic media assist in rapidly answering questions related to patient care, most residents, fellows, and experienced clinicians still use the printed word to comprehensively learn about a new topic, prepare for board examination and recertification, and even organize a clinical management plan for the patient with a complex array of co-existing diseases.

So in this setting, where does *Case-Based Anesthesia: Clinical Learning Guides* edited by Drs. Shorten, Dierdorf, O’Connor, Iohom, and Hogue fit in? In other words, do we need yet another anesthesiology text? The answer, in this case, is a resounding yes! Why? First starting with the title, *Clinical Learning Guides*, the editors have chosen to emphasize learning in the broader sense, not just Board exam preparation and re-certification, but acquisition of knowledge as part of the process of responsibility and accountability for one’s education and lifelong learning. By viewing education through this lens, the practitioner can apply information gained from this text into a variety of clinical and examination settings. The Editors accomplish their goal through the innovative approach of using two formats for case-based learning: “Step-by Step” or “Reflection.” This is a unique approach for a textbook. Importantly, it recognizes different learning styles to help reinforce important clinical concepts. This is the first time such diverse information has been organized on these educationally sound principles in a clinical textbook. The editors have coupled this with the use of “hot topics” where new evidence can be applied to clinical conundrums as well as to responses to examination questions. This is accomplished by a list of all-star contributors, each an authority in his/her own area of expertise. It is as if the reader is being taken through a clinically challenge case with an expert at their side.

As Thomas L. Friedman implies in his best-selling book *The World is Flat* (Picador 2007), anesthesiologists worldwide are truly interconnected, as globalization brings us into wide-reaching contact with our peers and new opportunities arise. Thus, *Case-Based Anesthesia: Clinical Learning Guides* is targeted at an international array of inquisitive trainees and clinicians whose basic goal is safe and unsurpassed clinical care of our patients.

Paul G. Barash, MD  
Professor, Department of Anesthesiology  
Yale University School of Medicine  
Attending Anesthesiologist  
Yale-New Haven Hospital  
New Haven, Connecticut





# CONTRIBUTORS

**Hassan M. Ahmad, MD**

*The Johns Hopkins School of Medicine  
The Johns Hopkins Hospital  
Baltimore, Maryland*

**Ioanna Apostolidou, MD**

*Associate Professor of Anesthesiology  
School of Medicine  
University of Minnesota  
Minneapolis, Minnesota*

**Ashit Bardhan, MBBS, FCARCSI**

*Specialist Registrar  
Cork University Hospital  
Cork, Ireland*

**Dorothy Breen, FCARCSI, FJFICM**

*Specialist Registrar in Anaesthesia  
Cork University Hospital  
Cork, Ireland*

**Siun Burke, FCARCSI**

*Research Fellow  
Cork University Hospital  
Cork, Ireland*

**Asokumar Buvanendran, MD**

*Associate Professor of Anesthesiology  
Rush University Medical Center  
Chicago, Illinois*

**Charles D. Collard**

*Professor and Vice-Chairman  
Department of Anesthesiology  
Baylor College of Medicine  
Houston, Texas*

**W. Christopher Croley, MD, FCCP**

*Assistant Professor of Anesthesiology and Critical Care Medicine  
Rush University Medical Center  
Chicago, Illinois*

**Stephen F. Dierdorf, MD**

*Professor and Vice Chairman  
Department of Anesthesia  
Indiana University School of Medicine  
Indianapolis, Indiana*

**John Dowling, BDS, MB, BCh, BAO(Hons),  
BMedSc(NUI)**

*Specialist Registrar in Anaesthesia  
Cork University Hospital  
Cork, Ireland*

**Craig Dunlop, MBBS, FCARCSI**

*Specialist Registrar in Anaesthesia  
Cork University Hospital  
Cork, Ireland*

**Amanda A. Fox**

*Staff Anesthesiologist  
Brigham & Women's Hospital  
Harvard Medical School  
Boston, Massachusetts*

**Kelly Grogan, MD**

*Assistant Professor of Anesthesiology and Critical Care Medicine  
The Johns Hopkins School of Medicine  
The Johns Hopkins Hospital  
Baltimore, Maryland*

**Anthony Hennessy, FCARCSI**

*Specialist Registrar in Anaesthesia  
Cork University Hospital  
Cork, Ireland*

**Charles W. Hogue, Jr., MD**

*Associate Professor  
Department of Anesthesiology and Critical Care Medicine  
The Johns Hopkins Medical Institutions and The Johns Hopkins Hospital  
Baltimore, Maryland*

**Michelle Isac, MD**

*Assistant Clinical Professor of Anesthesia  
McMaster University  
Hamilton, Ontario, Canada*

**Jason S. Johnson, MD**

*Associate Professor of Anesthesiology  
School of Medicine  
University of Minnesota  
Minneapolis, Minnesota*

**Roy Kan, MBBS(Singapore), MMed (Anesth)**

*Department of Anesthesiology and Critical Care Medicine  
The Johns Hopkins School of Medicine  
The Johns Hopkins Hospital  
Baltimore, Maryland*

**Justin Lane, FCARCSI**

*Specialist Registrar in Anaesthesia  
Cork University Hospital  
Cork, Ireland*

**Peter John Lee, MB, BCh, BAO, FCARCSI**

*Specialist Registrar in Anaesthesia  
Cork University Hospital  
Cork, Ireland*

**Audrey R. Leverich, MD**

*Fellow in Cardiothoracic Anesthesiology  
Department of Anesthesiology  
Weill Cornell Medical College  
New York-Presbyterian Hospital  
New York, New York*

**Jay K. Levin, MD**

*Department of Anesthesiology and Critical Care Medicine  
The Johns Hopkins School of Medicine  
The Johns Hopkins Hospital  
Baltimore, Maryland*

**Bryan V. May, MD**

*Southeast Anesthesiology Consultants  
Charlotte, North Carolina*

**Nanhi Mitter, MD**

*Assistant Professor  
Department of Anesthesiology  
Rush University Medical Center  
Chicago, Illinois*

**Laurel E. Moore, M.D.**

*Department of Anesthesiology  
The University of Michigan  
Ann Arbor, Michigan*

**Mohan Mugawar, FCARCSI**

*Specialist Registrar in Anaesthesia  
Department of Anaesthesia  
Cork University Hospital  
Cork, Ireland*

**Christopher J. O'Connor, MD**

*Professor of Anesthesiology  
Rush University Medical Center  
Chicago, Illinois*

**Brian D. O'Donnell, MB, FCARCSI, MSc**

*Clinical Lecturer in Anaesthesia  
Cork University Hospital  
Cork, Ireland*

**James O'Driscoll, FCARCSI**

*Specialist Registrar in Anaesthesia  
Cork University Hospital  
Cork, Ireland*

**Owen O'Sullivan, MB, BCh, BAO**

*Specialist Registrar in Anaesthesia  
Cork University Hospital  
Cork, Ireland*

**Richard J. Pollard, MD**

*Southeast Anesthesia Consultants  
Charlotte, North Carolina*

**David M. Rothenberg, MD, FCCM**

*The Max S. Sadove, MD Professor of Anesthesiology  
Associate Dean, Academic Affiliations  
Rush University Medical Center  
Chicago, Illinois*

**Leon Serfontein, MBChB, FANZCA**

*Consultant Anaesthetist  
Cork University Hospital  
Cork, Ireland*

**Mansoor A. Siddiqui, MBBS, FCPS, FCARCSI**

*Specialist Registrar in Anaesthesia  
Cork University Hospital  
Cork, Ireland*

**Nikolaos J. Skubas, MD**

*Associate Professor of Anesthesiology  
Weill Cornell Medical College  
Department of Anesthesiology  
New York, New York*

**Joshua D. Stearns, MD**

*Assistant Professor of Anesthesiology and Critical Care Medicine  
The Johns Hopkins School of Medicine  
The Johns Hopkins Hospital  
Baltimore, Maryland*

**Jason Van der Velde, BAA, MBChB, EMDM-A**

*Trauma Research Registrar  
Cork University Hospital  
Cork, Ireland*

**John Vullo, MD**

*Southeast Anesthesiology Consultants  
Charlotte, North Carolina*

**Adrienne Wells, MD**

*Assistant Professor of Anesthesiology  
Rush University Medical Center  
Chicago, Illinois*

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# Statins and Perioperative Risk

Amanda A. Fox and Charles D. Collard

## CASE FORMAT: REFLECTION

A 75-year-old, 50-kg, Caucasian female presented for left heart cardiac catheterization after having a positive finding on a dobutamine stress echocardiogram. She had a history of exertional chest pain, hypertension, dyslipidemia, and a 45 pack-year history of cigarette smoking. The patient's history was also significant for peripheral vascular disease, with bilateral lower extremity claudication. A right carotid endarterectomy (CEA) was performed in 2002. The patient's serum creatinine level was 1.3 mg/dL, with an estimated creatinine clearance of 30 mL/min. She was receiving the following medications: intravenous nitroglycerin and heparin infusions, atenolol 25 mg orally once per day, and aspirin 81 mg orally once per day.

Cardiac catheterization revealed significant three-vessel coronary artery disease (90% proximal left main coronary artery, 90% proximal right coronary artery, 60% first obtuse marginal) and a left ventricular ejection fraction of 60%. Carotid ultrasound showed no significant stenosis of the right carotid artery, but there was 85% to 90% stenosis of the left proximal internal carotid artery. Thus, the patient was scheduled for combined left CEA and coronary artery bypass graft (CABG) surgery.

On the day of surgery, a right radial arterial line was placed preinduction with midazolam sedation and local anesthesia. The patient then underwent intravenous induction of anesthesia with 8 mg of midazolam, 100 mg of thiopental, 200 µg of fentanyl, and 10 mg of pancuronium. Anesthesia was maintained with 0.6% to 0.8% end-tidal isoflurane. A right internal jugular central line was placed. Electroencephalogram monitoring was conducted throughout the CEA without evidence of complications. Three-vessel CABG surgery was performed (left internal mammary arterial conduit to the left main artery and saphenous vein grafts to the right coronary artery and first obtuse marginal artery), and the patient was separated uneventfully from cardiopulmonary bypass. After heparin reversal with protamine and chest closure, the surgeons closed the left CEA neck incision. The patient was extubated 3 hours after surgery and had an uneventful postoperative course. She was monitored for 24 hours in the intensive care unit and was then transferred to the hospital ward. The patient's postoperative serum creatinine peaked at 1.6 mg/dL and returned to her preoperative value of 1.3 mg/dL before discharge. The patient was discharged to home on postoperative day 7, at which time in addition to her previous preoperative medications, she was started on rosuvastatin 5 mg orally per day.

## CASE DISCUSSION

### Pharmacologic Mechanisms of Statins

3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, commonly known as *statins*, are frequently prescribed cholesterol-lowering medications that decrease circulating plasma low-density lipoprotein (LDL) cholesterol. Statins are not only associated with reduced atherosclerotic plaque formation, but there is mounting evidence that statins may help prevent atherosclerotic plaque rupture.<sup>1</sup> Atherosclerotic plaques that are vulnerable to rupture have a prothrombotic, lipid-rich core that is infiltrated with active macrophages and is covered by a thin fibrous cap. Surgical insults such as trauma to tissues, vascular cross clamping, extracorporeal circulation, or blood transfusion can trigger profound systemic proinflammatory responses that may prompt vulnerable plaque rupture resulting in arterial occlusion and end-organ ischemia (e.g., myocardial infarction [MI], stroke, renal and gastrointestinal infarction). Potential mechanisms by which statins may stabilize vulnerable plaques, as well as reduce the impact of plaque rupture include:

1. Increasing the collagen content of the lipid-rich plaque core.<sup>2</sup>
2. Decreasing plaque macrophage content<sup>2</sup> and T-cell activity.<sup>2,3</sup>
3. Inhibition of cellular matrix metalloproteinases involved with erosion of the fibrous plaque cap.<sup>2,4</sup>
4. Inhibition of cellular transcription factors that modify G proteins involved in regulating endothelial, leukocyte, and platelet function.<sup>4</sup>
5. Decreasing inflammatory mediators such as interleukin-6, C-reactive protein, tumor necrosis factor- $\alpha$ , and serum amyloid A.<sup>3,5</sup>

Thus, the benefits of statin therapy are not limited to cholesterol alone, and statin therapy in the perioperative setting may be particularly beneficial because of antiatherosclerotic, anti-inflammatory, and antithrombotic properties. However, the precise underlying mechanisms by which statins prevent or reduce adverse postoperative outcomes, such as mortality or postoperative atrial fibrillation, are not yet clearly defined.<sup>6</sup>

### Perioperative Statins: The Evidence in Cardiac and Vascular Surgery

A recent meta-analysis of 223,010 patients undergoing cardiovascular surgery found that preoperative statin therapy was associated with 38% and 59% reductions in the risk of 30-day

mortality after cardiac (1.9% vs. 3.1%;  $p = 0.0001$ ) and vascular (1.7% vs. 6.1%;  $p = 0.0001$ ) surgery, respectively.<sup>7</sup> Additionally, a retrospective, case-control study of more than 2600 primary, elective CABG surgery patients found that preoperative statin therapy was independently associated with a reduced risk of in-hospital cardiovascular death (adjusted odds ratio [OR], 0.25; 95% confidence interval [CI], 0.07–0.87) but not nonfatal postoperative MI.<sup>8</sup> Thus, perioperative statin therapy has been shown to be associated with a reduced incidence of acute, in-hospital adverse outcomes.

However, the benefits of perioperative statin therapy extend beyond the acute perioperative period. For example, a study of post-CABG surgery patients with moderately elevated LDL cholesterol levels who were placed on aggressive, long-term lovastatin therapy (goal LDL concentration <100 mg/dL) showed that during the 4-year follow-up period after starting statin therapy, patients on aggressive therapy experienced significantly reduced saphenous vein graft occlusion and need for revascularization as compared with patients on lower-dose statin therapy.<sup>9</sup> This clinical observation is also supported by in vitro evidence that statins prolong arterial bypass graft patency.<sup>10</sup> Finally, at least one retrospective study suggests that statin therapy may slow the progression of bioprosthetic aortic valve degeneration after surgical implantation.<sup>11</sup>

Cardiovascular morbidity and mortality after vascular surgery is also relatively frequent, with mortality and nonfatal MI occurring in up to 5% to 6% and 30% of patients, respectively.<sup>1</sup> Retrospective studies of preoperative statin therapy in patients undergoing major vascular surgery have shown that statins are associated with a reduced risk in both in-hospital and long-term, all-cause cardiovascular mortality.<sup>12,13</sup> Additionally, a recent prospective randomized study of vascular surgery patients found that preoperative atorvastatin therapy significantly reduced adverse cardiovascular events up to 6 months after surgery.<sup>14</sup> Based on these data, it seems reasonable that the patient who underwent combined major cardiac and vascular surgery in the case presentation might have benefited from statin therapy initiated preoperatively.

## Perioperative Statins: The Evidence in Noncardiovascular Surgery

Although the present case involves both major cardiac and vascular surgery, cardiovascular complications after noncardiac surgery are also an important cause of morbidity and mortality. A recent retrospective cohort study investigated the association between perioperative statin therapy and in-hospital postoperative mortality in 780,591 patients undergoing major noncardiac surgery at 329 hospitals in the United States. Moreover, this study only assessed patients whose preoperative statin therapy was reinitiated within 2 days after surgery, and it found that perioperative statin therapy was associated with a significant reduction in all-cause mortality (adjusted OR, 0.62; 95% CI, 0.58–0.67).<sup>15</sup> Not only do these data further suggest the usefulness of preoperative statin therapy, but they also suggest the importance of continuing statins throughout the postoperative period.

## Effect of Statin Withdrawal

In a study of ambulatory patients, statin therapy initiated before the occurrence of acute MI was associated with a signifi-

cantly decreased incidence of adverse cardiovascular events.<sup>16</sup> If statin therapy was discontinued after the MI occurred, however, the incidence of 30-day death and nonfatal MI was significantly increased compared with patients receiving continuous statin therapy (OR, 2.93; 95% CI, 1.64–6.27).<sup>16</sup> This finding may explain in part why studies of the benefits of preoperative statin therapy have reported mixed results regarding postoperative nonfatal MI outcomes, as many of these surgical studies did not assess whether statins were continued in the postoperative period. Supporting this hypothesis is a recent multicenter study of 2666 CABG surgical patients in which preoperative statin therapy was independently associated with a significant reduction (adjusted OR, 0.25; 95% CI, 0.07–0.87) in the risk of cardiac death within the first 3 days following primary, elective CABG surgery (0.3 vs. 1.4%;  $p < 0.03$ ) but was not associated with a reduced risk of postoperative nonfatal, in-hospital MI (7.9% vs. 6.2%;  $p = \text{NS}$ ). In this same study, however, discontinuation of statin therapy after surgery was independently associated with a significant increase in late (postoperative day 4 though hospital discharge) all-cause mortality (adjusted OR, 2.64; 95% CI, 1.32–5.26) as compared with patients in whom statin therapy was continued (2.64 vs. 0.60%;  $p < 0.01$ ). This was true even after controlling for the postoperative discontinuation of aspirin,  $\beta$ -blockers, or angiotensin-converting enzyme inhibitor therapy. Discontinuation of statin therapy after surgery was also independently associated with a significant increase in late, in-hospital cardiac mortality (adjusted OR, 2.95; 95% CI, 1.31–6.66) compared with patients in whom statin therapy was continued (1.91% vs. 0.45%;  $p < 0.01$ ).<sup>8</sup>

Despite guidelines by the American College of Cardiology and American Heart Association recommending statin therapy for CABG patients with LDL concentrations >100 mg/dL,<sup>17</sup> two thirds of such patients may not be receiving statin therapy when discharged from the hospital after their CABG surgeries.<sup>18</sup> Reasons for not initiating or reinitiating statin therapy after CABG surgery may include patients' decreased tolerance of oral medications secondary to postoperative nausea and vomiting, transient renal dysfunction, concerns pertaining to hepatic toxicity or myositis, or failure of the responsible physician to reimplement preoperative medications. Thus, it may be warranted to educate physicians about the potential benefits of perioperative statin therapy that continue in the postoperative period. In the present case, although the patient was discharged on rosuvastatin, not only was she not receiving preoperative statin therapy, but there was also failure to initiate a statin in the immediate preoperative period. Both are measures that might have decreased her risk for both in-hospital and long-term adverse cardiovascular outcomes.

## 2007 American College of Cardiology and American Heart Association Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery

In light of the previously mentioned evidence, the American College of Cardiology and the American Heart Association recently published perioperative guidelines that for the first



time specifically address the role of perioperative statin therapy.<sup>19</sup> Specifically, these new guidelines state that:

1. For patients currently taking statins and scheduled for noncardiac surgery, statins should be continued.<sup>19</sup>
2. For patients undergoing vascular surgery with or without clinical risk factors, statin use is reasonable.<sup>19</sup>
3. For patients with at least one clinical risk factor who are undergoing intermediate-risk procedures, statins may be considered.<sup>19</sup>

Thus, based on these guidelines, it would have been reasonable to initiate and maintain statin therapy throughout the perioperative period for the patient in the case presentation.

## Safety of Statin Therapy

Severe hepatotoxicity or myopathy associated with statin use has been reported but is rare.<sup>20</sup> This is true for all available statins, although the risk profile for atorvastatin might be the most favorable.<sup>20</sup> Although mild, dose-related elevations in serum aspartate aminotransferase and alanine aminotransferase occur in about 1% of patients on statins, and acute liver injury has been isolated to a few cases.<sup>21</sup> Although statins are considered contraindicated in patients with chronic liver disease, a recent multicenter, randomized, double-blind, placebo-controlled trial of pravastatin therapy in hyperlipidemic patients with chronic, compensated liver disease showed no increase in statin-associated hepatotoxicity in these patients.<sup>21</sup> Caution should be exercised in initiating statin therapy in patients with chronic liver disease, however, and should probably only be done in conference with such patients' gastroenterologists.

The most serious potential statin side effect is rhabdomyolysis. Across a spectrum of ambulatory trials, rhabdomyolysis was reported to occur in  $\leq 0.7\%$  of patients receiving a broad range of statins and doses.<sup>22</sup> Cerivastatin, which is no longer on the market, is known to have the greatest associated rhabdomyolysis risk (3.16 per million prescriptions).<sup>20</sup> In contrast, the risk of statin-related rhabdomyolysis is only in the range of 0 to 0.19 per million prescriptions for other commonly used statins.<sup>20</sup> The risk for rhabdomyolysis is associated with factors that increase serum statin concentrations, such as small body size, advanced age, renal or hepatic dysfunction, diabetes, hypothyroidism, and drugs that interfere with statin metabolism, such as cyclosporin, antifungal agents, calcium-channel blockers, and amiodarone.<sup>20</sup> Because these characteristics are prevalent in surgical populations, it is advisable to monitor for statin side effects in patients on perioperative statin therapy, particularly in those with muscle disease, or hepatic or renal dysfunction. The present case involving a small, elderly patient with renal insufficiency should have been closely monitored in the acute perioperative period for evidence of acidosis, muscle pain or weakness, or a rise in creatinine kinase level.

Although statin-related rhabdomyolysis is extremely rare, early recognition and treatment are important to avoid serious morbidity. In a recent study by Schouten et al., perioperative statin use was not associated with an increased risk of perioperative myopathy or increased postoperative creatine

phosphokinase concentrations in a large group of major vascular surgical patients.<sup>23</sup> After correcting for cardiac risk factors and clinical risk factors for myopathy, length of surgery remained the only independent predictor for myopathy.<sup>23</sup> No case of rhabdomyolysis was observed, and there was no difference in creatine phosphokinase levels between patients on long-term preoperative statin therapy and patients who started statin therapy shortly before surgery.<sup>23</sup>

## Need for Future Studies

Presently available data and guidelines suggest that perioperative statin therapy is both appropriate and beneficial, but further studies are needed to determine optimal statin duration and dosage. For example, although a recent meta-analysis of more than 300,000 patients with an acute MI suggests that initiating statin therapy within 24 hours of MI onset reduces mortality, it is not clear if this holds true for cardiovascular surgical patients with acute coronary syndromes, if they require longer periods of statin administration.<sup>24</sup> There thus remains a need for further randomized controlled trials conducted in specific cardiac and noncardiac surgical populations to identify patients who will benefit most from perioperative statin therapy and to determine the optimal duration of perioperative statin therapy.

### KEY MESSAGES

1. Statin administration is associated with decreased atherosclerotic plaque formation and may contribute to prevention of atherosclerotic plaque rupture.
2. A recent meta-analysis demonstrated that preoperative statin therapy was associated with a 38% and 59% reduction in the risk of 30-day mortality after cardiac (1.9% vs. 3.1%;  $p = 0.0001$ ) and vascular (1.7% vs. 6.1%;  $p = 0.0001$ ) surgery, respectively.
3. Perioperative statin therapy is associated with a reduced incidence of acute, in-hospital adverse outcomes.
4. Preoperative atorvastatin therapy significantly reduces adverse cardiovascular events up to 6 months after vascular surgery.
5. Following noncardiac surgery, perioperative statin therapy is associated with a significant reduction in all-cause mortality.
6. American College of Cardiology/American Heart Association guidelines state:
  - a. For patients currently taking statins and scheduled for noncardiac surgery, statins should be continued.
  - b. For patients undergoing vascular surgery with or without clinical risk factors, statin use is reasonable.
  - c. For patients with at least one clinical risk factor who are undergoing intermediate-risk procedures, statins may be considered.

## QUESTIONS

1. What is the mechanism by which statins lower circulating LDL cholesterol?

Answer: They act as inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase.

2. How do statins stabilize atheromatous plaques or limit the adverse effects of rupture?

Answer: Suggested mechanisms include:

Increasing the collagen content of the lipid-rich plaque core.

Decreasing plaque macrophage content<sup>2</sup> and T-cell activity.

Inhibition of cellular matrix metalloproteinases involved with erosion of the fibrous plaque cap.

Inhibition of cellular transcription factors that modify G proteins involved in regulating endothelial, leukocyte, and platelet function.

Decreasing inflammatory mediators such as interleukin-6, C-reactive protein, tumor necrosis factor- $\alpha$ , and serum amyloid A.

3. What adverse effects are associated with statin administration?

Answer: The most serious potential statin side effect is rhabdomyolysis. Mild, dose-related elevations in serum aspartate aminotransferase and alanine aminotransferase occur in about 1% of patients on statins; acute liver injury has been observed in a few cases. Severe hepatotoxicity or myopathy is rare.

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# Perioperative $\beta$ -Blockade

Stephen F. Dierdorf

## CASE FORMAT: STEP BY STEP

A 67-year-old male was scheduled for an exploratory laparotomy and probable colectomy for colon cancer. The patient had first noticed blood in his stool 4 months before the scheduled surgery, but he had only sought medical attention 2 weeks prior to surgery. Colonoscopy performed at that time revealed a mass in the descending colon, and a biopsy result was positive for adenocarcinoma. He was scheduled for surgery at the first available date. The patient had a 24-year history of hypertension treated with lisinopril and a 12-year history of non-insulin-dependent diabetes treated with diet and an oral hypoglycemic agent. He denied chest pain or exertional dyspnea. The patient, a retired accountant with a sedentary lifestyle, underwent a lumbar laminectomy and spinal fusion at age 53.

The patient's vital signs were as follows: heart rate, 86 beats per minute; blood pressure, 152/95 mm Hg; and respiratory rate, 16 breaths per minute. His height was 70 inches (1.8 meters), and his weight was 225 pounds (102 kg). Laboratory studies indicated that his resting electrocardiogram reading was normal; hematocrit level, 41%; sodium, 137 mmol/L; potassium, 4.1 mmol/L; creatinine, 1.2 mg/dL; blood urea nitrogen, 13 mg/dL; and glucose, 130 mg/dL.

The patient's internist recommended perioperative metoprolol. Would this reduce the patient's perioperative risk of an adverse cardiac event?

Ischemic heart disease is the major cause of morbidity and mortality in developed countries throughout the world. Approximately 100 million adults undergo noncardiac surgery per year, and 500,000 to 1 million will suffer a perioperative cardiac complication. The efficacy of  $\beta$ -blockers for the treatment of ischemic heart disease is well documented, and it is only logical that  $\beta$ -blocker therapy should be applied to patients with coronary artery disease undergoing noncardiac surgery.

Surgery produces an increase in stress hormones and catecholamine levels and a hypercoagulable state. Effects of these increases include tachycardia, hypertension, enhanced myocardial contractility, and increased myocardial oxygen demand. In susceptible patients, adverse cardiac events such as myocardial ischemia and dysrhythmias can occur.  $\beta$ -Adrenergic blockers reduce myocardial oxygen demand by reducing heart rate, cardiac contractility, and blood pressure. Slowing of the heart rate increases diastole

and allows more time for coronary artery filling.  $\beta$ -Blockers also act at the cellular level to improve the balance between oxygen supply and demand by protecting myocardial mitochondria by means of antioxidation. All of these effects can reduce the incidence of perioperative myocardial ischemia and cardiac dysrhythmias.

Although the initial report of the efficacy of  $\beta$ -blockers to reduce perioperative cardiac events was published in 1987, two studies from the 1990s sparked widespread interest in perioperative  $\beta$ -blockers.<sup>1-3</sup> By 2002, the indications for the administration of perioperative  $\beta$ -blockers had been expanded.<sup>4,5</sup>

The patient's internist recommended the oral administration of long-acting metoprolol for 72 hours before surgery. Intravenous metoprolol was to be administered if the patient's heart rate was greater than 65 beats per minute immediately before surgery. In the preoperative holding area, the patient's heart rate was 76 beats per minute, and his blood pressure was 138/80 mm Hg. After intravenous metoprolol (5 mg), his heart rate was 63 beats per minute, and his blood pressure was 124/68 mm Hg.

## Are there differences in the pharmacologic effects of different $\beta$ -blockers?

Although differences in the effects of different  $\beta$ -blockers have been demonstrated in basic research and animal studies, there have been no compelling reports of clinically significant differences.  $\beta$ -1 and  $\beta$ -2 receptors are found in cardiac muscle; however,  $\beta$ -1 receptors are dominant.  $\beta$ -2 Receptors are the primary  $\beta$ -receptors in bronchi.

Propranolol, a first-generation  $\beta$ -blocker, is a nonselective antagonist with equal antagonistic effects on  $\beta$ -1 and  $\beta$ -2 receptors. Second-generation  $\beta$ -blockers such as atenolol, metoprolol, and bisoprolol have much greater selectivity for blockade of  $\beta$ -1 receptors. Third-generation  $\beta$ -blockers such as labetalol, carvedilol, and nebivolol have varying  $\beta$ -adrenergic blocking effects ( $\beta$ -1 and  $\beta$ -2) and vasodilating capabilities. Labetalol is a nonselective  $\beta$ -blocker with strong  $\beta$ -1 receptor blocking effects thereby causing vasodilation. Carvedilol blocks  $\beta$ -1 and  $\beta$ -2 receptors. Nebivolol is a highly selective antagonist of  $\beta$ -1 receptors and causes vasodilation by activation of L-arginine and nitric oxide (Table 2.1). For diabetic patients, carvedilol increases insulin sensitivity, whereas atenolol and metoprolol decrease insulin sensitivity.<sup>6</sup> The lack of  $\beta$ -selectivity of propranolol and labetalol explains the increased incidence of bronchoconstriction with both drugs.

**TABLE 2.1**  $\beta$ -Adrenergic Antagonists

<b>First-generation <math>\beta</math>-blockers</b>
Propranolol
<b>Second-generation <math>\beta</math>-blockers</b>
Metoprolol
Atenolol
Bisoprolol
<b>Third-generation <math>\beta</math>-blockers</b>
Labetalol
Bucindolol
Carvedilol
Nebivolol

Bisoprolol, metoprolol, and carvedilol have been shown to significantly reduce mortality in patients with heart failure. No clinical studies have been performed that demonstrate the superiority of one  $\beta$ -blocker over the others with respect to reducing perioperative risk. Limited evidence suggests that  $\beta$ -blockers with vasodilating properties may be better for patients after myocardial infarction and for patients with chronic ischemic heart disease.

Induction of anesthesia was performed with propofol (1.5 mg/kg), and rocuronium (0.6 mg/kg) was administered to facilitate tracheal intubation. Oxygen in sevoflurane was administered by face mask until adequate muscle relaxation was achieved for tracheal intubation. Direct laryngoscopy and tracheal intubation were performed without difficulty. The patient's vital signs immediately after tracheal intubation were: heart rate 68 beats per minute and blood pressure 80/45 mm Hg. Two 5-mg doses of ephedrine did not significantly affect the heart rate or blood pressure. Phenylephrine (100  $\mu$ g) increased the blood pressure to 100/60 mm Hg and decreased the heart rate to 58 beats per minute. Maintenance of anesthesia was done with desflurane in an air-oxygen mixture. The operative course was marked by blood pressure lability that required a phenylephrine infusion and repeated boluses of intravenous fluids to maintain a satisfactory blood pressure. Emergence was slower than expected, but the patient was extubated in the operating room without difficulty. He was confused for the first 48 hours after surgery. At the time of discharge from the hospital, his wife felt that he had returned to his normal mental status.

### Are there risks to perioperative $\beta$ -adrenergic blockade?

Aggressive  $\beta$ -blockade can cause bradycardia as well as hypotension and may increase the risk of stroke and death. The enthusiasm for widespread perioperative  $\beta$ -blocker administration has been dampened by reports concerning the lack of effect of  $\beta$ -blockers in some studies and an increased risk of adverse effects reported in others.<sup>7-9</sup> Studies such as these that report conflicting results present a dilemma for the clinical

anesthesiologist. Advisory and regulatory groups have been quick to advocate routine  $\beta$ -blocker therapy for a large number of patients. Unfortunately, data have been accumulating faster than these groups can revise guidelines.

### Can the differences in outcome from these studies be resolved to formulate a logical plan for perioperative $\beta$ -blocker therapy that has the highest benefit potential?

Resolving three questions concerning perioperative  $\beta$ -blockade would provide much-needed information.

1. Do current  $\beta$ -blocker regimens provide maximal cardioprotection?

Administration of  $\beta$ -blockers for 7 to 10 days before surgery may be required for optimal effect at the cellular level. This period of time may also be important for patients with hypertension to normalize cerebral autoregulation. Cooperative efforts among internists, surgeons, and anesthesiologists would be required to achieve this goal.

2. Is more precise perioperative hemodynamic control required?

There is evidence that  $\beta$ -blockade and tight heart rate control are associated with a lower incidence of myocardial ischemia and better long-term outcome.<sup>10</sup>

3. Are there differences in individual patients that explain the inconsistencies in the results from published studies?

Polymorphism in adrenergic receptors may affect a patient's response to  $\beta$ -blockers and have a significant effect on ultimate outcome. It is known that patients with hypertension have a variable response to  $\beta$ -blockers based on genetic variations in adrenergic receptors. Ser49Gly and Arg389Gly are two single nucleotide polymorphisms of  $\beta$ 1-adrenergic receptor genes. Patients with hypertension and Arg389Arg receptors have a greater decrease in systolic and diastolic blood pressure when treated with metoprolol.<sup>11</sup> A study of patients undergoing surgery with spinal anesthesia found that the polymorphism of the  $\beta$ -adrenergic receptor was more predictive of outcome than the influence of  $\beta$ -blockers.<sup>12</sup> Because no previous perioperative studies evaluated genetic variations, differences in genetic patterns might explain variable responses to  $\beta$ -blockers. Further study of the relationship between perioperative outcome and genetic variations in adrenergic receptors is clearly warranted.

### This patient had no adverse perioperative cardiac events but did have significant blood pressure lability and possible central nervous system morbidity (delayed emergence and postoperative confusion). Was he, in fact, a suitable candidate for perioperative $\beta$ -blockers?

Recommendations for treatment can be divided into three classes based on risk-to-benefit ratio and degree of evidence.

- Class I: benefit  $\gg \gg$  risk. Treatment should be administered.  
 Class IIa: benefit  $\gg$  risk. It is reasonable to administer treatment.  
 Class IIb: benefit  $\geq$  risk. Treatment may be considered.  
 Class III: risk  $\geq$  benefit. Treatment should not be administered.

**TABLE 2.2** Risk for Noncardiac Surgery

<b>Low-risk surgery</b>
Ambulatory surgery
Breast surgery
Cataract surgery
Endoscopy (gastrointestinal and gastric ulcers)
<b>Intermediate risk surgery</b>
Intraperitoneal surgery
Intrathoracic surgery
Carotid endarterectomy
Head and neck surgery
Orthopedic surgery
<b>High-risk surgery</b>
Aortic surgery
Peripheral vascular surgery

Patients require stratification regarding preoperative medical condition and degree of risk of the surgery (Table 2.1). Patients receiving preoperative  $\beta$ -blockers for cardiac disease should have  $\beta$ -blockers continued regardless of the risk of surgery (class I). High-risk patients undergoing vascular surgery should also receive perioperative  $\beta$ -blockers (class I).<sup>13</sup> There are several risk factors for adverse perioperative outcomes (Table 2.2). Patients with active cardiac diseases such as unstable angina, recent myocardial infarction, heart failure, significant dysrhythmias (high-grade atrioventricular block), and severe valvular disease require evaluation and treatment prior to noncardiac surgery. Provocative testing for myocardial ischemia need only be performed if testing will alter management (e.g., revascularization). Patients with only one or two risk factors undergoing intermediate risk surgery do not require stress testing but may benefit from perioperative  $\beta$ -blockers.

**The patient had two preoperative risk factors: hypertension and diabetes mellitus and was undergoing intermediate-risk surgery. The indication for perioperative  $\beta$ -blockers was weak and intraoperative hemodynamic instability did develop.**

Patients with risk factors for cardiac disease present many challenges for perioperative management. Recommendations

**TABLE 2.3** Cardiac Risk Factors

Ischemic heart disease
Compensated heart failure
Cerebrovascular disease
Diabetes mellitus
Renal insufficiency

for evaluation and management of the patient with some risk factors but no overt evidence of cardiac disease have not been sufficiently elucidated to provide the anesthesiologist with clear and unambiguous guidelines. It is difficult for advisory and regulatory groups to revise recommendations as rapidly as new information accumulates. Although  $\beta$ -blockers can certainly reduce the incidence of perioperative cardiac events, there are potential risks, and accurate patient stratification is necessary to obtain maximum benefit with the least risk.<sup>14</sup> The effect of the perioperative use of statins and  $\alpha$ -2 adrenergic agonists on outcome needs to be more thoroughly evaluated. The judicious use of these drugs in combination with  $\beta$ -blockers may achieve an even greater perioperative risk reduction (Table 2.3).<sup>15</sup>

### KEY MESSAGES

1.  $\beta$ -Adrenergic blockers produce pharmacologic effects that can reduce the incidence of perioperative myocardial ischemia and cardiac dysrhythmias. These effects include decreasing myocardial oxygen demand by reducing heart rate, cardiac contractility, and blood pressure; slowing of the heart rate to prolong diastole during which coronary artery flow occurs; and protection of myocardial mitochondria by means of antioxidation.
2. No clinical studies have been performed that demonstrate the superiority of one  $\beta$ -blocker over the others with respect to reducing perioperative risk.
3. Administration of  $\beta$ -blockers for 7 to 10 days before surgery may be required for optimal effect at the cellular level.

### QUESTIONS

1. By what mechanism do  $\beta$ -adrenergic blockers reduce the risk of myocardial ischemia?  
Answer:  $\beta$ -blockers reduce myocardial oxygen consumption by reducing heart rate, myocardial contractility, blood pressure, and protecting mitochondria by antioxidation. The reduction in heart rate increases diastole and provides more time for coronary perfusion.
2. What does class IIB recommendation imply?  
Answer: Treatment recommendations are based on strength of evidence supporting a treatment. A class IIB recommendation suggests that enough evidence exists that a treatment should be considered.
3. What are the risks of perioperative  $\beta$ -adrenergic blockade?  
Answer: Although perioperative  $\beta$ -adrenergic blockade can reduce the incidence of myocardial ischemia, the risk of intraoperative hypotension, stroke, and death are increased.

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# Perioperative Glycemic Control

Kelly Grogan

## CASE FORMAT: REFLECTION

A 72-year-old male with a history of type 2 diabetes mellitus, hypertension, and remote tobacco use presented for coronary artery bypass graft surgery. His medications included aspirin daily, metoprolol 50 mg daily, metformin 500 mg twice daily, omeprazole 20 mg daily, and atorvastatin 10 mg daily. He had no known drug allergies. Preoperatively, an echocardiogram showed mild mitral regurgitation, nonsignificant aortic sclerosis, and a left ventricular ejection fraction of 40% with mild inferior hypokinesis. Laboratory test results included a fasting serum glucose level of 165 mg/dL; HgbA1C, 7.6%; hematocrit, 36%; and creatinine, 1.3 mg/dL. On the morning of surgery, the patient's serum glucose level was 134 mg/dL. He had received metoprolol the morning of surgery, and was fasting since 10:00 PM on the previous evening.

After induction of general anesthesia and tracheal intubation, central venous access was obtained, and a transesophageal echocardiography probe was placed. The patient's initial serum glucose level was 155 mg/dL. An intravenous insulin infusion was started at 2 units per hour. Serum glucose testing was repeated every hour during the procedure, and the insulin dosage was adjusted based on the institutional intraoperative insulin protocol (Table 3.1).

### What is the epidemiology of diabetes mellitus?

From 1980 through 2004, the number of Americans with diabetes mellitus increased from 5.8 to 14.7 million. Diabetes now affects nearly 21 million Americans, or 7% of the U.S. population; more than 6 million of the affected do not know they have diabetes. Compelling evidence continues to accumulate suggesting that poorly controlled glucose levels are associated with increased morbidity and mortality rates, as well as higher health care costs. Further, long-term strict glycemic control reduces the frequency of diabetes complications, particularly microvascular complications and renal dysfunction. The United States spends approximately \$132 billion each year on diabetes—\$92 billion in direct medical costs and another \$40 billion in indirect costs because of missed workdays or other losses in productivity.<sup>1</sup>

### What is (are) the relationship(s) between the mechanisms underlying hyperglycemia and poor patient outcome?

The mechanisms of harm from hyperglycemia center on the immune system, mediators of inflammation, vascular perturbations, altered hemodynamics, and enhanced neuronal damage following brain ischemia. The association of hyperglycemia and infection appears to primarily result from phagocyte dysfunction involving impaired neutrophil and monocyte adherence, chemotaxis, phagocytosis, and bacterial killing.<sup>2</sup> Classic microvascular complications of diabetes are caused by alterations in the aldose reductase pathway, advanced glycation end-product pathway, enhanced reactive oxygen species production, and the protein kinase C pathway. Several of these pathways may contribute to immune dysfunction.<sup>3</sup>

Acute hyperglycemia also has numerous effects on the cardiovascular system. Hyperglycemia impairs myocardial ischemic preconditioning that might contribute to larger myocardial infarct size in diabetics compared with nondiabetics.<sup>4</sup> Hyperglycemia is associated with reduced coronary collateral blood flow<sup>5</sup> and increased cardiac myocyte death through apoptosis<sup>6</sup> or by exaggerating ischemia-reperfusion cellular injury.<sup>7</sup> Multiple studies have identified a variety of hyperglycemia-related abnormalities in hemostasis that favor thrombosis.<sup>8,9</sup>

Acute hyperglycemia is associated with enhanced neuronal damage following induced brain ischemia.<sup>2</sup> This enhanced injury is mostly in the ischemic penumbra thus contributing to stroke expansion.<sup>10–13</sup> Elevated glucose concentrations have been associated with enhanced cerebral ischemic damage secondary to increased tissue acidosis and lactate levels. Lactate has been associated with damage to neurons, astrocytes, and endothelial cells.<sup>14</sup>

### Other than glycemic regulation, how does insulin influence metabolic regulation?

There may be beneficial effects of insulin therapy that are separate from mere glycemic control. First, insulin inhibits lipolysis, reducing free fatty acid levels that are believed to contribute to cardiac arrhythmias. Next, insulin stimulates endothelial nitric oxide synthase enhancing nitric oxide secretion, resulting in arterial vasodilation in addition to a variety of other beneficial effects on oxidation and inflammation. Finally, insulin, in the environment of euglycemia or near-euglycemia,

**TABLE 3.1A** Insulin Loading Dose and Initial Infusion Rate

Glucose (mg/dL)	Recommended Action	
	Intravenous Loading Bolus	Infusion Rate
>300	12 units	8–10 U/h
261–300	9 units	7–8 U/h
231–260	7 units	6–7 U/h
201–230	3 units	5–6 U/h
171–200	2 units	3–5 U/h
141–170	0 units	2–3 U/h
120–140	0 units	1–2 U/h
100–119	0 units	0.5 U/h

appears to inhibit proinflammatory cytokines, adhesion molecules, and chemokines, in addition to acute-phase proteins.<sup>15</sup>

### Is in-hospital hyperglycemia associated with adverse patient outcomes?

Data from observational studies have linked hyperglycemia with poor outcome in acutely ill patients. In cardiac surgical patients, hyperglycemia is associated with a greater risk for sternal wound infections.<sup>16,17</sup> More aggressive treatment of hyperglycemia with intravenous insulin targeting serum glucose levels of 100 to 150 mg/dL reduced the risk of deep sternal wound infections by 57% compared with historical controls in which the goal was to maintain glucose levels between 150 to 200 mg/dL.<sup>18,19</sup> In those analyses, there was a

significant correlation between average postoperative glucose level and mortality with the lowest mortality rates found in patients with postoperative glucose levels <150 mg/dL. In patients undergoing general surgery, a single blood glucose level >220 mg/dL is associated with a nearly threefold greater risk for infection compared with blood glucose levels <220 mg/dL.<sup>20</sup> Multiple other retrospective studies have linked hyperglycemia with worse outcomes in patients with acute myocardial infarction.<sup>21,22</sup> Hyperglycemia is further associated with more severe brain damage and mortality after ischemic but not hemorrhagic stroke.<sup>23,24</sup>

Until recently, data linking hyperglycemia with poor outcomes in hospitalized patients were retrospective. In a landmark series of prospectively randomized, double-blinded studies, Van den Berghe et al.<sup>25</sup> reported that criti-

**TABLE 3.1B** Insulin Dose for Infusion Titration Based on Hourly Glucose Checks

Glucose (mg/dL)	Rising Glucose		Falling Glucose	
	Re-Bolus	Increase Rate	Hold Infusion	Decrease Rate
>350	12 units	5–6 U/h	—	0%
301–350	9 units	4–5 U/h	—	0%
251–300	7 units	3–4 U/h	—	0%
201–250	5 units	2–3 U/h	—	0%–10%
161–200	3 units	1–2 U/h	—	0%–10%
121–160	0 units	No change	0–30 min	0%–25%
81–120	0 units	No change	0–60 min	0%–50%
61–80	0 units	No change	0–60 min	25%–75%
40–60		Stop infusion; ensure adequate glucose administration	30–60 min	Do not restart infusion until glucose is >120 mg/dL
<40		Stop infusion; administer one-half amp D50 and check glucose in 30–60 min	Until adequate rebound in glucose is ensured	Do not restart infusion until glucose is >120 mg/dL



cally ill patients in a mixed medical surgical intensive care unit (ICU) had improved outcomes with intensive insulin therapy targeted to serum glucose levels of 80 to 110 mg/dL compared with standard treatment. Patients in the intensive insulin treatment group had a 34% reduction in mortality, a 46% lower incidence of sepsis, a 41% reduction in the rate of renal failure requiring dialysis, a 50% reduction in the frequency of blood transfusion, and a 44% reduction in the rate of critical illness polyneuropathy compared with the control group. These benefits, however, were restricted to patients hospitalized in the ICU for 3 to 5 days. When the data were limited to medical ICU patients, intensive insulin treatment was associated with worse outcomes, in fact, for patients with a shorter duration of ICU admission. A meta-analysis of 35 clinical trials evaluating the effect of insulin therapy on mortality rates in hospitalized patients with critical illness found that insulin therapy decreased short-term mortality by 15% in a variety of clinical settings.<sup>26</sup> These studies, however, did not investigate the risk versus benefits of intraoperative intensive insulin management. In fact, Gandhi et al.<sup>27</sup> found a higher mortality rate for patients randomized to receiving intensive insulin therapy (targeted glucose levels of 80 to 110 mg/dL) during cardiac surgery compared with controls.

### What glucose level should be targeted?

Based on the available data, recommendations have been advanced as to what serum glucose level to target with insulin therapy for patients in critical care settings. The targets for non-intensive care patients including those during surgery are less well defined and are somewhat controversial. Regardless, guidelines from the American Diabetes Association and the American College of Endocrinology recommend intensive insulin management for both ICU and non-ICU patients (Table 3.2).<sup>15,28</sup> Guidelines for the management of patients with acute stroke from the American Heart Association, however, acknowledge that the exact glucose level that should be targeted with insulin therapy for patients with stroke are not known and are probably <140 mg/dL.<sup>29</sup>

**TABLE 3.2** Recommended Targets for Serum Glucose Levels in Hospitalized Patients from the ADA and the ACE

	<b>ADA (28)</b>	<b>ACE (15)</b>
Intensive care unit	As close to 110 mg/dL as possible	<110 mg/dL
Non-critical care units	As close to 90–130 mg/dL as possible; maximal <180 mg/dL	<110 mg/dL preprandial; maximal <180 mg/dL

To convert mg/dL of glucose to mmol/L, divide by 18 or multiply by 0.055.

ACE, American College of Endocrinology; ADA, American Diabetes Association.

### What are the principles of perioperative management of the diabetic patient?

Insulin resistance and insulin secretory capacity in hospitalized patients is influenced by numerous factors, including severity of illness, medications (e.g., glucocorticoids and catecholamines), procedures, and diet that is often interrupted. The ability to control glucose in diabetic patients will, in part, depend on the quality of their control before admission. This can be assessed by measuring hemoglobin A1C value (a value >6% indicates poor control).

Hospitalized patients are usually not managed with oral hypoglycemic agents because of their long half-life, potential for side effects caused by an acute illness, and the inability to rapidly titrate the dose. Nonetheless, continuing oral hypoglycemic agents taken before hospitalization is considered for non-critically ill patients who had good pre-hospital glucose control and who are expected to eat a normal diet. Important considerations for the use of oral hypoglycemic agents in hospitalized patients include:

- Sulfonylureas have a long duration of action (that varies from patient to patient) predisposing to hypoglycemia especially in patients who are not eating (nothing by mouth [NPO]). These agents do not allow rapid dose adjustment to meet the changing needs of acutely ill patients. Further, sulfonylureas block ATP-sensitive potassium channels that mediate in part myocardial ischemic preconditioning. Patients at risk for myocardial ischemia, thus, might experience greater myocardial damage if given sulfonylureas (e.g., during cardiac surgery or when a perioperative myocardial infarction occurs).
- Metformin may lead to potentially fatal lactic acidosis particularly during the stress associated with surgery or acute illness. Risk factors for this side effect include cardiac disease, heart failure, hypoperfusion, renal insufficiency, old age, and chronic pulmonary disease. Nonetheless, predicting individual susceptibility is limited, and most data regarding this condition are from case series in which other factors might have confounded the findings. Regardless, metformin is typically stopped the morning of surgery or at least 8 hours before surgery.
- Thiazolidinediones have few side effects, but these drugs do increase intravascular volume that might predispose to congestive heart failure. Their use is associated with abnormal liver function tests, and they should not be given to patients with liver dysfunction.

Previously diagnosed and newly diagnosed diabetics will likely require insulin management perioperatively or during an acute illness. The commonly used “sliding scale insulin therapy” with regular insulin is generally inappropriate as a sole insulin management strategy. A key component to providing effective insulin therapy is determining whether a patient has the ability to produce endogenous insulin. Patients with type 1 diabetes are by definition insulin deficient. Patients with prior pancreatectomy or with pancreatic dysfunction, those who have received insulin for greater than 5 years, and patients with wide fluctuations in serum glucose levels may all have a significant degree of insulin deficiency. Patients determined to be insulin deficient require basal insulin replacement at all times to prevent iatrogenic diabetic

ketoacidosis. A subcutaneous insulin regimen consists of three elements:

- Basal insulin requirement provided in the form of intermediate or long-acting analogs such as lente insulin. Some non-insulin-deficient patients may not require basal insulin if they are to take nothing by mouth. However, withholding basal insulin in insulin-deficient patients may result in ketoacidosis.
- Prandial insulin is given before meals. The rapid-acting insulin analogs, insulin lispro and aspart, are excellent prandial insulins. Some patients do receive their prandial coverage immediately after eating, and the dose is based on carbohydrate counting.
- Correction-dose or supplemental insulin is given to treat hyperglycemia. This should not be confused with “sliding scale insulin,” which usually refers to a set amount of insulin administered for hyperglycemia without regard to the timing of food, the presence or absence of pre-existing insulin administration, or individualization of the patient’s sensitivity to insulin. Correctional-dose insulin can be used to accommodate the increased insulin requirements that accompany acute illness and insulin resistance secondary to counterregulatory responses to stress and/or illness.

By far, intravenous insulin is the most reliable means for achieving glycemic control particularly in critically ill patients who may have severe or rapidly changing insulin requirements, generalized edema, impaired perfusion of subcutaneous sites and extremities, and those who are receiving total parenteral nutrition and/or sympathomimetic drugs. Most institutions now have standardized algorithms. The most effective are those that use dynamic scales, incorporating the rate of change in glucose into dose adjustments. Frequent glucose level monitoring is imperative to ensure good control and minimize hypoglycemic events. As a patient’s clinical status improves, he or she can be transitioned to subcutaneous insulin. This step requires using the most recent infusion rate to approximate the overall daily requirement, dividing this into basal and prandial components. It is often necessary to overlap the intravenous and subcutaneous insulin to ensure a proper conversion.

## PREVENTION AND MANAGEMENT OF HYPOGLYCEMIA

Hypoglycemia, if unrecognized and prolonged, can have severe and permanent negative outcomes. Hospitalized patients are at an increased risk of developing hypoglycemia because of altered nutritional state, liver and kidney dysfunction, infection, malignancy, and sepsis. Changes in medications (particularly steroids and catecholamines), decreased oral intake, vomiting, procedures that require the patient to take nothing by mouth, unexpected interruptions of enteral feedings or parenteral nutrition, and patients’ mental status all contribute to the complexity of glucose management. Patients that are sedated or under general anesthesia, having delirium, or are hospitalized for neurologic events will be unable to communicate the typical signs and symptoms of hypoglycemia. Decreased levels of consciousness, confusion, or diaphoresis may be the only signs. Acute hypoglycemia is treated by administering 25 to 50 g of glucose intravenously.

## KEY MESSAGES

1. Diabetes now affects nearly 21 million Americans, or 7% of the U.S. population.
2. The mechanisms of harm from hyperglycemia center on the immune system, mediators of inflammation, vascular perturbations, altered hemodynamics, and enhanced neuronal damage following brain ischemia.
3. Van den Berghe et al. reported that critically ill patients in a mixed medical surgical ICU had improved outcomes with intensive insulin therapy targeted to serum glucose levels of 80 to 110 mg/dL compared with standard treatment.
4. Intravenous insulin is the most reliable means for achieving glycemic control, particularly in critically ill patients.

## QUESTIONS

1. By what mechanism(s) does diabetes mellitus result in microvascular complications?

Answer: These mechanisms are alterations in the aldose reductase pathway, advanced glycation end-product pathway, enhanced reactive oxygen species production, and the protein kinase C pathway.

2. What is the most important adverse effect associated with metformin administration?

Answer: Metformin may lead to potentially fatal lactic acidosis, particularly during the stress associated with surgery or acute illness.

3. What factors may contribute to hypoglycemia in acutely ill patients?

Answer: Decreased nutritional intake (decreased oral intake, vomiting, procedures that require the patient to take nothing by mouth, unexpected interruptions of enteral feedings or parenteral nutrition, altered level of consciousness), liver and kidney dysfunction, infection, malignancy, and sepsis may be contributing factors.

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# Neuraxial Analgesic Techniques for Cardiac Anesthesia

Hassan M. Ahmad

## CASE FORMAT: STEP BY STEP

A 62-year-old, 85-kg man with a history of cigarette smoking, hypertension, and hyperlipidemia was referred by his primary care physician for a routine exercise stress test. Electrocardiogram changes occurred in the anterior leads when his heart rate was 50% of the maximal predicted rate, although the patient remained asymptomatic. He was then referred for diagnostic and possible interventional cardiac catheterization. Angiography confirmed the presence of a 90% distal stenosis of the left anterior descending coronary artery and a 75% stenosis of the circumflex coronary artery. Because the former lesion was not amenable to percutaneous intervention, he was referred for coronary artery bypass graft surgery (CABG).

During the preoperative interview, the cardiac anesthesiologist learned that the patient had an active lifestyle with frequent exercise and a past medical history of hypertension. His current medications were hydrochlorothiazide, atorvastatin, and aspirin. He had no known allergies and had undergone an appendectomy 20 years previously. The patient had been smoking one pack of cigarettes per day for approximately 40 years, and his family history was positive for coronary artery disease (both parents having suffered "heart attacks" in their late 50s). Physical examination revealed faint wheezing in both lung fields. Blood pressure was 142/67 mm Hg; heart rate, 72 beats per minute; room air oxygen saturation, 96%; and temperature, 36.7°C. All baseline investigations (hematology, chemistries, and coagulation studies) were normal.

The surgical plan was to perform a median sternotomy and "off-pump" CABG surgery with the left internal mammary artery to the left anterior descending artery and saphenous vein graft to the circumflex coronary artery. After a discussion with the patient, the anesthetic plan was combined general and thoracic epidural anesthesia.

### Are there benefits to epidural anesthesia and analgesia for cardiac surgery?

Several studies have compared general with combined general/epidural anesthesia for cardiac surgery. There is some evidence to indicate that the use of epidural analgesia facilitates early tracheal extubation postoperatively. Other outcomes, including duration of hospital stay and overall cost are similar when the two techniques are compared.<sup>6,7</sup>

The more theoretical benefits of epidural anesthesia/analgesia for cardiac surgery are related to sympathetic blockade. Decreased heart rate and coronary vasodilation result in improved subendocardial blood flow, which might be beneficial for patients undergoing CABG surgery. Attenuation of stress reactions and attenuation of postoperative pain are other proposed benefits. Several (although not all) investigations have suggested that postoperative sympathetic blockade decreases the incidence of atrial fibrillation typically on postoperative day 2 or 3 in greater than one third of patients. Overall, potential theoretical benefits of thoracic epidural anesthesia/analgesia for CABG surgery have not been shown to lead to clinically important patient benefit.<sup>8,9,10</sup>

On the morning of surgery, the patient was transported to the preoperative area, where the anesthesiologist inserted a thoracic epidural at the T5-6 level. A 17-gauge Tuohy needle was used to access the epidural space, utilizing a loss-of-resistance technique. An epidural catheter was inserted 4 cm into the epidural space, and a 3-mL test dose of 1.5% lidocaine with 1:200,000 epinephrine was administered with no evidence of intravascular or intrathecal injection.

### What are the potential risks and complications of using epidurals in cardiac surgery?

Placing an epidural before surgery requiring subsequent anticoagulation has been shown to be quite safe in several different settings. In general, the possibility of infection, bleeding, and nerve injury should be clearly disclosed to patients before placing an epidural catheter.<sup>2</sup>

The greatest concern in inserting an epidural prior to cardiac surgery is the potential risk of epidural hematoma secondary to anticoagulation. Large series indicate that epidural catheter placement before anticoagulation with unfractionated or low-molecular-weight heparin can be performed with a minimal risk for epidural hematoma if certain precautions are taken.

Other complications from epidural anesthesia include hypotension resulting from sympathectomy and systemic toxic effects of opioids and local anesthetics.

### What are the guidelines for the use of epidurals in the setting of anticoagulation with heparin?

It is not uncommon for patients undergoing cardiac surgery to have been on a heparin infusion before surgery. The American Society of Regional Anesthesia has issued guidelines that may reduce the risk of epidural hematoma related to epidurals in anticoagulated patients. Typically, heparin infusion should be

discontinued 4 hours before epidural placement, and the interval between epidural placement and complete anti-coagulation for bypass should exceed 60 minutes. Also, epidural catheters should be removed only when normal coagulation has been restored; if a heparin infusion is required in the postoperative period, the infusion should be discontinued 2 to 4 hours prior to catheter removal. In general, epidurals should be avoided in patients with known coagulopathy. It is unclear whether a traumatic epidural placement necessitates canceling cardiac surgery, but the consensus is to delay the operation for at least 24 hours, should a “bloody tap” occur.<sup>5</sup>

### Can intrathecal opioids be used for cardiac surgery?

It has been shown that inadequate analgesia in the postoperative period leads to increased likelihood of myocardial ischemia associated with the stress response to pain. Adverse changes in hemodynamics, metabolic activity, immune function, and hemostasis can be attenuated with better pain control.

Several studies have evaluated the potential benefit of intrathecal opioids as a method of providing postoperative analgesia. Most investigations have studied the use of intrathecal morphine and its effect on time to tracheal extubation, use of additional intravenous opioids, and duration of hospital stay. Generally, the long-acting effect of intrathecal morphine provided better analgesia compared to placebo. No clear benefit has been demonstrated regarding tracheal extubation and overall outcomes, however, in part because of the adverse respiratory effects. The combined use of intrathecal morphine and intrathecal clonidine provides better postoperative analgesia and facilitates earlier tracheal extubation.<sup>1</sup>

### What dosing regimen should be used?

The goals for an epidural technique in cardiac surgery are establishing surgical anesthesia, thereby minimizing systemic opioid use and to create a significant sympathectomy. This means a block level as high as T1.

The dosing should begin with a test dose of 1.5% lidocaine with epinephrine 1:200,000 to detect an unwanted intrathecal or intravascular catheter. Then, a loading dose of preservative-free morphine 20 µg/kg is given, followed by 0.5% bupivacaine given in 5-mg increments to a total of 25 to 35 mg. A continuous infusion of 0.5% bupivacaine with morphine 25 µg/mL is started at 4 mL per hour and adjusted to achieve adequate analgesia.

### Is the use of a total spinal technique justified?

Much of the proposed benefit of regional anesthesia in cardiac surgical patients is based on the sympathetic blockade, which cannot be reliably achieved with intrathecal opioids alone. Administration of large doses of intrathecal local anesthetics to achieve this goal has been studied. Typically, the Trendelenburg position is used to achieve an adequate cephalad spread to above T1, resulting in a “total spinal.” Although the subsequent sympathectomy is observed by serum markers and hemodynamics, no significant clinical benefit results. Moreover, the resultant hypotension and bradycardia may make this technique inappropriate for cardiac surgical patients.<sup>4</sup>

### Are there any other regional techniques that can favorably influence the postoperative course?

Parasternal block entails the surgeon injecting local anesthetic along the sternal border to anesthetize the intercostal nerves and their branches. Using this technique has been shown to significantly decrease the dose of morphine required in the immediate postoperative period and was associated with better oxygenation at the time of tracheal extubation (although not an earlier time of extubation). Nonetheless, it is a relatively safe and easy procedure that can provide excellent analgesia.<sup>3</sup>

#### KEY MESSAGES

1. Epidural analgesia and anesthesia is an option in cardiac surgery and has the potential for earlier extubation and improved pain control in the immediate postoperative period.
2. The complete systemic anticoagulation associated with cardiopulmonary bypass is a concern with placement of epidural catheters, particularly the risk of developing an epidural hematoma.
3. A combination of local anesthetics and opioids can be administered via epidural, and there are several potential effects related to the attenuated stress response that may be beneficial to cardiac surgical patients.

#### QUESTIONS

1. What spinal levels are associated with sympathetic nervous supply to the heart?  
Answer: T1-T5.
2. What are the early clinical signs of epidural hematoma?  
Answer: Back pain, lower extremity weakness and diminished sensation, and loss of bowel and bladder control.
3. What long-acting local anesthetic has been shown to have less cardiovascular toxicity than bupivacaine?  
Answer: Ropivacaine

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# Off-Pump Coronary Artery Surgery

Audrey R. Leverich and Nikolaos J. Skubas

## CASE FORMAT: STEP BY STEP

A 62-year-old man with triple-vessel coronary artery disease presented for off-pump coronary artery bypass graft surgery (OPCAB). His past medical history included hypertension and hyperlipidemia. A coronary angiogram revealed a 95% obstruction of the left anterior descending artery (LAD), 60% stenosis of the circumflex artery (CX), and 70% narrowing of the right coronary artery (RCA). Left ventricular (LV) ejection fraction was preserved (>50%); there was mild mitral regurgitation, and LV pressures were 135/12 mm Hg. Carotid ultrasound revealed 80% obstruction of the right carotid artery. Physical examination, vital signs, and laboratory work were within normal limits, except for a bruit audible over the right side of the patient's neck. His medication list included an antihypertensive, a  $\beta$ -blocker, aspirin, and a statin.

### How does OPCAB differ from CABG?

Standard coronary revascularization procedures in the past relied on the use of extracorporeal circulation (cardiopulmonary bypass [CPB]). The use of CPB during CABG surgery, however, is associated with undesirable effects including coagulation abnormalities, activation of the inflammatory response, and the potential for multiple organ system dysfunction. OPCAB involves performing coronary revascularization on a beating heart.<sup>1</sup> High-risk patients such as those who have cerebral, renal, or pulmonary dysfunction as well as the elderly (>80 years), might likely benefit the most from OPCAB by avoiding the deleterious consequences of CPB. Patients with severe atherosclerosis of the ascending aortas might further benefit from OPCAB because aortic cross clamping is not necessary. Contraindications to OPCAB are mostly limited to technical considerations such as an intramyocardial coronary artery that is difficult to dissect, intracavitary thrombus that can be dislodged during heart manipulation, and combined surgical procedures that include open-chamber valve replacement surgery. Patients with a history of malignant ventricular arrhythmias, as well as patients who would not tolerate periods of myocardial ischemia, are not optimal candidates for OPCAB procedures (Table 5.1).

### What are the surgical approaches to OPCAB?

There are two surgical approaches to OPCAB: (a) the minimally invasive direct access coronary artery bypass graft (MID-CAB) procedure, which involves a small left thoracotomy

incision, through which the left internal mammary artery (LIMA) is anastomosed to the target vessel (usually the LAD); and (b) the typical OPCAB in which multiple coronary artery bypass grafts are constructed via a median sternotomy incision. Exposure of the target coronary vessels is achieved with displacement of the heart.<sup>2</sup> The LAD, diagonal branches, and proximal RCA can be adequately exposed with a suction stabilizer device and sponges in the pericardial sac (Fig. 5.1), and the displacement is minimal. Targets in the posterior (distal RCA) and lateral (CX) surface of the heart, however, require rotating the heart out of the thoracic cavity with anterior displacement ("verticalization"). This is typically achieved with an aspirating device placed on the cardiac apex. In either case, stabilizing the epicardium is necessary to carry out coronary arteriotomy and graft anastomosis. Stabilizer devices use a combination of pressure and suction to immobilize the planned anastomotic site (Fig. 5.2). Transient interruption of coronary flow is achieved with elasticized sutures placed around the proximal and distal target vessel. Anastomoses are then performed on a relatively bloodless, motionless field.

### Does the patient's history affect the anesthesia plan?

This patient has extensive coronary artery disease, but his LV function is preserved, and there are no significant valvular lesions. The presence and degree of collateral coronary blood supply should dictate the sequence of distal anastomoses. The presence of a carotid bruit at the site of a documented carotid stenosis raises concerns regarding preservation of cerebral blood flow to the brain perioperatively. For these reasons, hypotension may not be tolerated in this patient. This patient might further have atherosclerosis of the ascending aorta or of other arteries such as the renal and splanchnic arteries (Fig. 5.3). Blood flow to the latter might be sensitive to reduce blood pressure during cardiac manipulations while OPCAB is being performed.

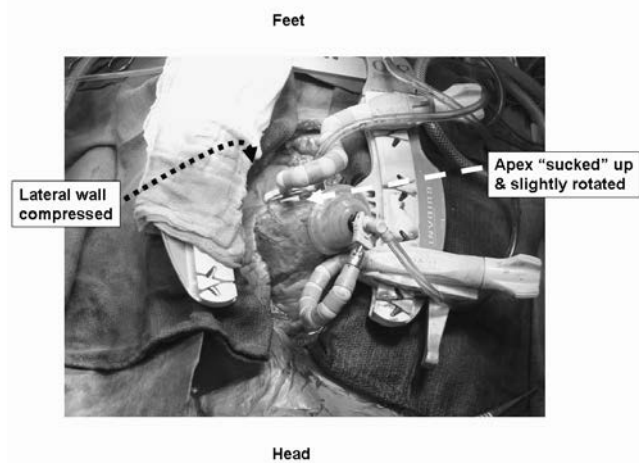
### Which monitors should be used during the intraoperative period?

Conventional five-lead electrocardiogram (ECG), pulse oximetry, and intra-arterial blood pressure monitoring should be performed in all patients undergoing an OPCAB procedure. In addition, a pulmonary artery catheter can be considered depending on ventricular function, pulmonary arterial hypertension, or other complicating factors. External defibrillator/pacing pads should be placed particularly for MIDCAB where

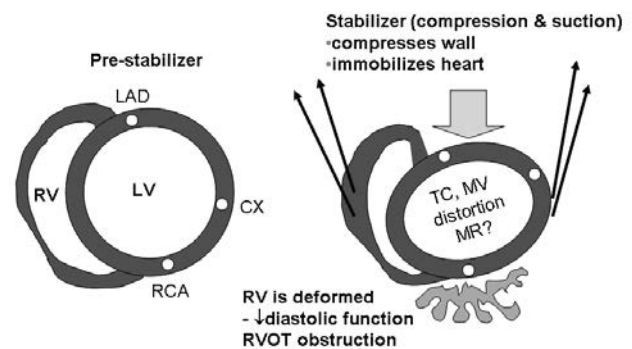
**TABLE 5.1** Differences Between Traditional CABG and OPCAB

	<b>CABG</b>	<b>OPCAB</b>
Incision	Sternotomy	Sternotomy or Thoracotomy
Heparinization	Full: ACT >480 s	Partial: ACT ~250–300 s
Cannulation	Aortic, venous	Neither
Aortic cross clamp	Yes	No
Cardioplegia	Yes	No
Partial aortic cross clamp for construction of proximal anastomosis	Yes	Yes, if > two vessels No, if all arterial grafts on a “Y” or “T” anastomosis to LITA

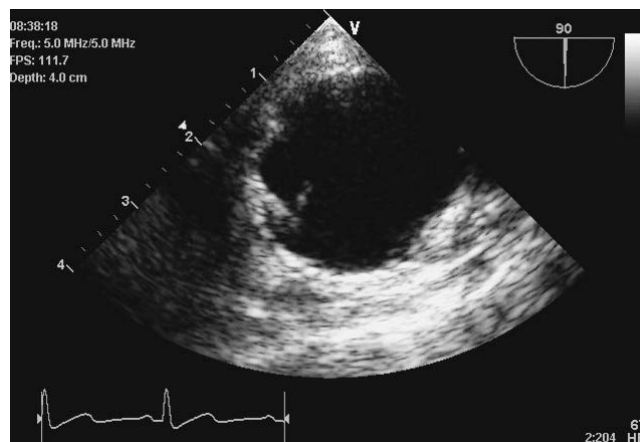
ACT, activated clotting time; CABG, coronary artery bypass graft; LIMA, left internal mammary artery; OPCAB, off-pump coronary artery bypass graft surgery.



**Figure 5.1 • A Stabilizer Device Used for Off-Pump Coronary Revascularization.** A combination of suction (applied to the cardiac apex) and stabilization (applied at the anastomotic site; here at the lateral wall of the heart) provides an immobile and bloodless field.



**Figure 5.2 •** The stabilizer device pushes on the left ventricular (LV) wall, restricts local motion, and decreases LV dimensions; their contribution to SV is predominant. Compression of the anterior and lateral walls has more serious hemodynamic consequences than compression of the inferior (posterior) wall. The most profound disturbances are observed during lateral wall exposure for anastomosis on the left circumflex coronary artery (CX). LAD, left anterior descending coronary artery; MR, mitral regurgitation; MV, mitral valve; RCA, right coronary artery; RV, right ventricle; RVOT, right ventricular outflow obstruction; TC, tricuspid valve.



**Figure 5.3 •** Upper esophageal short axis view of the aortic arch demonstrating a protruding atheroma (grade V) at 7 o'clock.



exposure of the heart is necessary for internal defibrillation or when cardioversion is limited.<sup>1</sup> For this particular patient, intraoperative transesophageal echocardiography (TEE) would allow not only monitoring of volume status and evaluation of cardiac performance, but also examination of the aorta for the presence of atheromas. When interpreting hemodynamic data, the position of the heart must be taken into account. Surgical manipulation of the heart changes its relationship to the ECG electrodes, making it difficult to interpret the ST segments. Similarly, surgical maneuvers affect pulmonary artery catheter readings. Distortion of the heart, particularly verticalization, causes elevations in right atrial and pulmonary wedge pressures<sup>8</sup>. The vertical position of the heart, along with the interposition of air between the heart and esophagus, reduces the quality of TEE images during OPCAB procedures. However, most TEE images remain interpretable and are extremely valuable in the diagnosis of new regional wall motion abnormalities, ventricular function, and volume status.

### What is the best anesthetic plan for this patient?

Most commonly, a conventional general anesthetic technique is used during OPCAB procedures.<sup>1</sup> Because the postoperative course is accelerated in the majority of OPCAB patients, the anesthetic technique should be tailored to facilitate early tracheal extubation. The agents' duration of action should be considered when choosing opioids, neuromuscular blockers, and hypnotics. Additionally, every effort should be made to avoid hypothermia. Room temperature should be maintained around 24°C, fluids should be warmed, and a heat-moisture exchanger should be included in the ventilator circuit. New generations of circulating water warming mattresses might minimize heat loss. Forced air warmers can be used when saphenous vein harvest is not performed (or after completion). In some centers, thoracic epidural anesthesia/analgesia is used as an adjunct to general anesthesia. Epidural anesthesia reduces myocardial oxygen demand and increases supply by dilating epicardial vessels and improving collateral blood flow. The routine use of antifibrinolytics is not recommended during OPCAB, because of the potential trend toward a hypercoagulable state. "Full heparinization," with an activated clotting time (ACT) above 400 seconds, is not required during OPCAB procedures because patients are not exposed to the foreign surface of the bypass circuit. However, the patient's coagulation system will be activated by local vascular endothelial injury.<sup>6</sup> Therefore, some degree of anticoagulation is required. Heparin in a dose of 100 to 200 units per kilogram is given before dissection of the LIMA targeting an ACT of 250 to 300 seconds.

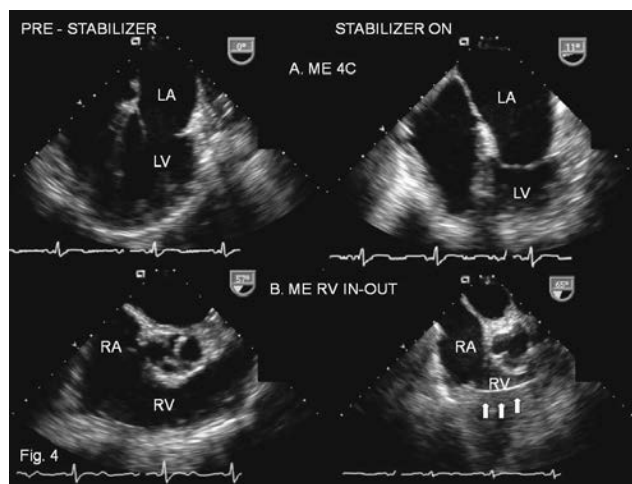
### Can anesthetic management affect patient outcome after OPCAB?

After the LIMA is harvested, the target coronary arteries are prepared for distal anastomoses. The risk of myocardial ischemia is greatest during anastomosis of the least collateralized vessel, whereas highly collateralized vessels are less at risk.<sup>5</sup> The most stenotic artery is therefore usually the first vessel to be revascularized. Before performing the anastomosis, the surgeon may induce a short period of myocardial ischemia by temporarily occluding the target vessel with an elasticized

suture and then allowing the myocardium to be reperfused. This step is believed to induce ischemic preconditioning, in which the myocardium may build up a tolerance to subsequent ischemia. Additionally, the use of volatile anesthetic agents 30 minutes before vessel occlusion may protect the myocardium against ischemia via anesthetic preconditioning. Early clinical data in patients undergoing CABG surgery, however, suggest that high concentrations (2 MAC) of volatile anesthetics are needed to significantly reduce troponin I release.<sup>4</sup> While the coronary artery is occluded, a favorable myocardial oxygen balance is essential.  $\beta$ -Blockers and calcium-channel antagonists are used to decrease heart rate and myocardial contractility, thereby decreasing myocardial oxygen consumption. Vasopressors, such as phenylephrine and norepinephrine, are used to maintain oxygen supply by increasing coronary perfusion pressure. In most patients, a mean arterial pressure of 70 mm Hg or higher is adequate to preserve coronary flow. It is important to remember that, once the target vessel is opened, the surgical anastomosis must be completed despite any hemodynamic derangements. The surgeon might consider placing a temporary coronary artery shunt.

### What hemodynamic changes should the anesthesiologist be prepared to treat/prevent?

During coronary artery bypass graft anastomosis, the anesthesiologist must manage the hemodynamic changes caused by distortion of the heart. During vertical displacement, the ventricles become positioned above the atria; TEE may reveal an increase in atrial size and a decrease in ventricular size (Fig. 5.4). Because blood must now flow against gravity and resistance, atrial filling pressures must be maintained at a higher level to preserve ventricular filling. In addition, the



**Figure 5.4** • Cardiac chamber compression with application of a stabilizer device (STABILIZER ON) for off-pump coronary artery bypass. (A) In the midesophageal four-chamber (ME 4C) view, application of the stabilizer device results in compression of the left ventricular (LV) cavity and elongation of the left atrium (LA). (B) The right ventricle (RV) is compressed during application of the stabilizer for construction of the right coronary arterial bypass graft. Notice the near elimination of the RV cavity at end-diastole (arrows). RA, right atrium.

heart may be compressed within the chest during vertical and lateral displacement. The right ventricle may become wedged between the left ventricle and the right pericardium, and complete right ventricular outflow obstruction may occur. Volume loading and Trendelenburg positioning serve to increase preload. The surgeon may release the right pericardium to allow adequate space for the right ventricle during this maneuver. Manipulating the heart's position may cause mitral regurgitation. Rotation and verticalization of the heart distorts the mitral valve annulus, causing it to twist and fold over on itself.<sup>3</sup> TEE evaluation may reveal new (or more severe) regurgitation. Large "V" waves may appear on the pulmonary artery catheter tracing. Abnormal mitral valves are more prone to distortion and are more likely to become functionally stenotic during cardiac manipulations for OPCAB. This phenomenon is also seen with distortion of the tricuspid valve and less often with the aortic valve. Stabilizing the epicardium during coronary artery anastomosis causes local distortion of the ventricle. The immobilizing device pushes on the myocardium and restricts wall motion. Because the anterior and lateral walls supply a major portion of stroke volume, their compression causes more severe reduction in cardiac output than when other portions of the ventricle are compressed. The most extreme hemodynamic compromise occurs during CX anastomosis, in which the heart is significantly elevated and perfusion of the lateral wall is compromised. Bradycardia is common during surgical manipulation, particularly during RCA anastomosis. Complete atrioventricular block can occur. The surgeon should consider placing temporary pacemaker wires before occluding the RCA. Additionally, a defibrillator/cardioverter should be available for the treatment of malignant arrhythmias.

### What are the indications for conversion to CPB?

Even with aggressive management, up to 5% of patients cannot tolerate the hemodynamic alterations caused by OPCAB. A cardiac index  $<1.5$  liters/minute per  $m^2$ , mean arterial pressure  $<50$  mm Hg, or a mixed venous saturation  $<60\%$  may not be tolerated for more than 15 minutes. Persistent ST elevations  $>2$  mm or malignant ventricular arrhythmias also indicate the need for conversion from an OPCAB to surgery using CPB.<sup>12</sup> A "dry" CPB machine, as well as a perfusion team, should be available during all OPCAB procedures.

### What hemodynamic abnormalities occur after reperfusion of the bypassed vessel?

Reperfusion injury may produce significant ECG changes, such as T-wave inversions or arrhythmias, during the first 30 minutes after coronary revascularization. Ventricular function should be evaluated after reperfusion with TEE. Persistent regional wall motion abnormalities predict poor postoperative outcome. Signs of continuing regional ischemia or poor flow through the bypass graft should prompt surgical intervention.

### Should heparin be reversed at the end of the case?

Because patients are not fully heparinized during OPCAB procedures, protamine reversal is not always required. Some institutions believe that the risk of a hypercoagulable state

after OPCAB might increase the risk for early bypass graft thrombosis. Most centers, however, use protamine to reduce the risk of postoperative bleeding and transfusions.

### Are patient outcomes affected by undergoing OPCAB versus on-pump CABG procedures?

In the immediate postoperative period, OPCAB patients experience a slightly accelerated recovery. They generally have less postoperative bleeding and receive fewer blood transfusions.<sup>10</sup> Preserving pulsatile blood flow, as well as avoiding hypothermia during OPCAB procedures might further contribute to accelerated recovery. The duration of hospitalization in the intensive care unit, as well as the overall hospital length of stay, is shortened with OPCAB surgery compared with traditional CABG surgery.<sup>9,11</sup> Hospital costs are therefore lower in the OPCAB patients. At 1 year, coronary angiography has demonstrated similar graft patency rates in OPCAB and on-pump CABG patients when experienced surgeons perform the surgery.<sup>9,11</sup> Five years postoperatively, rates of myocardial infarction, repeat coronary revascularization, stroke, and mortality are similar in both groups.<sup>13</sup> In low-risk patients, rates of neurocognitive dysfunction are similar in both OPCAB and on-pump patients. However, patients at high risk for poor neurologic outcome may benefit from OPCAB procedures.<sup>7</sup>

### KEY MESSAGES

1. Patients with severe atherosclerosis of the ascending aorta benefit from OPCAB because aortic cross clamping is not necessary.
2. During OPCAB, "full" heparinization (ACT  $>400$  seconds) is not required because patients are not exposed to the foreign surface of the CPB circuit. However, the patient's coagulation system will be activated by local vascular endothelial injury. Therefore, some degree of anticoagulation is required. Heparin in a dose of 100 to 200 units per kilogram is given before dissecting the LIMA targeting an ACT of 250 to 300 seconds.
3. Following OPCAB, persistent regional wall motion abnormalities are predictive of poor postoperative outcome.
4. Five years postoperatively, rates of myocardial infarction, repeat coronary revascularization, stroke, and mortality are similar among patients who undergo CABG on or off bypass.

### QUESTIONS

1. What surgical approaches are used to perform OPCAB?

Answer: There are two: (a) the MIDCAB approach involves a small left thoracotomy incision, through which the LIMA is anastomosed to the target vessel (usually the LAD) and (b) the typical OPCAB in which multiple

CABGs are constructed is performed via a median sternotomy.

## 2. What is the role of antifibrinolytic therapy in OPCAB?

Answer: The routine use of antifibrinolytics is not recommended during OPCAB, because of the potential trend toward a hypercoagulable state.

## 3. How does OPCAB compare with CABG with CPB in terms of graft patency?

Answer: At 1 year, coronary angiography has demonstrated similar graft patency rates in OPCAB and on-pump CABG patients when surgery is performed by experienced surgeons.

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# Aprotinin and Antifibrinolytics in Cardiac Surgery

Michelle Isaac

## CASE FORMAT: STEP BY STEP

A 79-year-old, 62-kg (body mass index, 22) female presented to the emergency department with severe chest pain and new ST-segment elevation in the inferior leads. She was referred for urgent cardiac catheterization. Angiography confirmed complete occlusion of the right coronary artery (RCA) as well as significant disease of the circumflex artery. The culprit RCA lesion was not amenable to percutaneous coronary intervention (PCI), and the patient was referred for urgent coronary artery bypass grafting (CABG).

Two years before this admission, the patient had undergone a PCI of the left anterior descending (LAD) artery with a drug-eluting stent. Her other medical history includes hypertension and hyperlipidemia for which she was receiving metoprolol and simvastatin. She is also receiving clopidogrel and aspirin since her PCI 2 years ago. Her temperature is 36.9°C; blood pressure, 135/76 mm Hg; heart rate, 65 beats per minute; and her respiratory rate, 18 breaths per minute. The patient's preoperative hemoglobin is 12.6 g/dL, platelet count, 253,000; international normalized ratio, 1.1; and prothrombin time, 29 seconds. Electrolytes, blood urea nitrogen, and creatinine are normal.

### Why is cardiac surgery associated with bleeding?

Surgery involving cardiopulmonary bypass (CPB) is associated with complex alterations to the hemostatic system resulting from hypothermia, hemodilution of hemostatic factors, consumption of coagulation factors caused by ongoing thrombin generation, fibrinolysis, platelet consumption and dysfunction, inadequate reversal of heparin, and heparin rebound after its reversal with protamine. In addition, the increasing use of newer anticoagulants such as low-molecular-weight heparins, direct thrombin inhibitors (e.g., hirudin, bivalirudin) and antiplatelet drugs (e.g., glycoprotein IIa/IIIb antagonist, clopidogrel) in patients presenting for cardiac surgery contributes to surgical bleeding.

### Is this patient at high risk for perioperative bleeding?

This patient's history suggests that she is at risk for perioperative bleeding. The continued use of clopidogrel is associated with higher rates of bleeding compared with patients not receiving antiplatelet drugs. Several studies have tried to

establish risk factors associated with nonsurgical bleeding after cardiac surgery to stratify patients and anticipate adverse outcomes. Identified risk factors include advanced age, female gender, nonelective cases, reoperation, complex surgeries, and smaller body mass index. Prolonged duration of CPB and surgery as well as persistent postoperative hypothermia are further key risk factors.

Before beginning the procedure, the cardiac surgeon, cardiac anesthesiologist, and perfusionist discuss their plans and concerns for this patient. They all agree that this patient is at high risk for perioperative bleeding and that there is a high likelihood that she will need transfusion of platelets after CPB because of her recent use of antiplatelet drugs. The blood bank is alerted to ensure that an adequate supply of packed red blood cells, fresh frozen plasma, and platelets is available.

### Why is prevention of bleeding important in cardiac surgery?

Perioperative bleeding results in risk for blood transfusion and re-exploration of the mediastinum because of continued bleeding or tamponade. Perioperative bleeding further results in transfusion of packed red blood cells and hemostatic factors. Blood transfusion is associated with infectious and noninfectious complications. The risk for viral transmission from massive transfusion has markedly decreased as a result of improved screening methods, although the risk for transmission of infectious agents persists (particularly, hepatitis C). Transmission of bacterial pathogens from packed red blood cells, and particularly platelet transfusion, is a higher risk than viral transmission. Other pertinent risks associated with blood transfusion include transfusion-related acute lung injury, volume overload, and hemolytic and nonhemolytic transfusion reactions. Further, limited supply of blood products necessitates that strategies be implemented to minimize transfusions.

### What is the incidence of reoperation in cardiac surgery, and what are its associated risks?

Resternotomy for postoperative bleeding is required in approximately 3% to 6% of cardiac surgical patients. The need for emergency mediastinal re-exploration is associated with increased length of intensive care unit stay, increased requirements for intra-aortic balloon counterpulsation, and increased mortality. Not surprisingly, many of the risk factors for resternotomy following cardiac surgery are the same as the risk factors identified for increased bleeding.

The surgical team has discussed blood conservation strategies for this patient, including the use of antifibrinolytic agents.

### **What pharmacologic approaches can be employed to reduce bleeding and transfusion requirements?**

Fibrinolysis is an important contributor to nonsurgical bleeding after cardiac surgery leading to not only breakdown of thrombus but also further consumption of hemostatic factors. The main pharmacologic treatment for preventing excessive bleeding during cardiac surgery is antifibrinolytic drugs such as tranexamic acid (TXA), epsilon-aminocaproic acid (EACA), and aprotinin. EACA and TXA are synthetic derivatives of the amino acid lysine. Lysine analogs inhibit the process of fibrinolysis by adhering to the lysine-binding site on plasminogen. Binding by lysine is required for the conversion of plasminogen to plasmin. Therefore, binding by these lysine analogs inhibits the formation of plasmin. Normally, plasmin causes fibrinolysis (lysis of clot) by degrading fibrin and fibrinogen. Not only is less plasmin generated, but existing plasmin is also inactivated. In contrast, aprotinin is a serine protease inhibitor which inhibits several important enzymes including plasmin and kallikrein. The exact mechanisms of aprotinin's action, however, are not completely understood.

### **What is the evidence for the efficacy of antifibrinolytic drugs?**

Several prospectively randomized, double-blind, placebo-controlled trials have been performed evaluating the efficacy of antifibrinolytics in cardiac surgery to reduce bleeding and blood transfusion. Many studies have been small, particularly those evaluating lysine analogs and those performing head-to-head comparisons of all three agents. Aprotinin has been the most well-studied agent. Several adequately powered, multicenter studies have established the efficacy of aprotinin to reduce bleeding, blood transfusion, and mediastinal reexploration for bleeding after cardiac surgery compared with placebo, particularly for complex cardiac surgeries or reoperations. These studies supported approval of aprotinin by the U.S. Food and Drug Administration for the indication of reducing bleeding during cardiac surgery.

Similar robust data are not present for TXA or EACA. Nonetheless, multiple studies have reported the efficacy of these agents to reduce bleeding complications of cardiac surgery. These data have been subjected to meta-analysis to enhance the power of the multiple small studies. A recent Cochrane review of antifibrinolytic drugs evaluated 51 trials showing that aprotinin use led to less chest tube drainage, fewer blood transfusions, and less need for reoperation for bleeding compared with placebo. Studies comparing TXA with placebo have also shown decreased requirement for blood product administration and mediastinal drainage but not mediastinal reexploration for bleeding. These results suggest that TXA results in savings of approximately one unit of allogeneic blood from being transfused compared with placebo. The amount of blood loss was reduced by approximately 300 mL with TXA use. Risk for reoperation was not affected by TXA. The small number of studies examining EACA in cardiac surgery has shown that its use

was associated with a relative 35% reduction in the need for allogeneic blood transfusion. The use of EACA resulted in a blood loss reduction of approximately 230 mL (intraoperatively) and 200 mL (postoperatively). Studies directly comparing EACA to TXA showed little difference between the two agents in terms of volume of blood transfused or reoperation for bleeding.

The cardiac anesthesiologist expressed concern about the safety of antifibrinolytics but agreed that the benefits in this high-risk patient likely outweighed the risks.

### **What are the risks associated with antifibrinolytics in cardiac surgery?**

Although the efficacy of aprotinin and the lysine analogs have been established, the safety of these agents in high-risk patients is more controversial. The safety of aprotinin, in particular, has been the focus of debate. Prospectively randomized, placebo-controlled studies have supported this agent's safety. These data, in fact, suggest aprotinin use was associated with a lowered risk for perioperative stroke compared with placebo. Aprotinin use is associated with a transient increase in serum creatinine that might reflect its effect on the proximal renal tubules. Because it is a bovine protein, allergic reactions to aprotinin are an established risk including fatal anaphylactic reactions. This risk has led to the use of a test dose, which can also trigger a severe response. Recent exposure (less than 1 year) is known to increase the likelihood of suffering from hypersensitivity reactions. For this reason, it is recommended that aprotinin should be used in settings where CPB can be established quickly.

Considering the mechanism of action of antifibrinolytic agents, it seems logical to expect they may increase the risk of thrombotic complications of surgery. The meta-analysis by the Cochrane Collaboration (which analyzed 211 randomized controlled trials) did not show increased risk of mortality, stroke, myocardial infarction, or deep vein thrombosis with aprotinin, TXA, or EACA. There was an increased trend toward renal dysfunction in the group receiving aprotinin, but this was not statistically significant.

The use of drugs during the well-controlled setting of a clinical trial might not adequately represent their safety profile compared with their widespread clinical use after approval. Of particular concern is attention to anticoagulation. Aprotinin prolongs the celite activated clotting time (ACT) regardless of the appropriate heparinization level. The use of a kaolin-based ACT, thus, is necessary when aprotinin is used and/or targeting higher levels of the ACT during surgery (>750 s). Moreover, in the "real world," other hemostatic agents might be coadministered with aprotinin in bleeding patients. The combined use of lysine analogs with aprotinin can result in intense inhibition of fibrinolysis. Further, the use of recombinant factor VIIa with aprotinin might promote prothrombotic complications. The safety of aprotinin was recently questioned in a recent retrospective analysis of data obtained in a multicenter study. This analysis suggested that patients receiving aprotinin during cardiac surgery had a higher risk for myocardial infarction, stroke, renal dysfunction, and death compared with lysine analog antifibrinolytics. The retrospective study design cannot exclude treatment bias whereby patients given aprotinin were at a higher risk for adverse outcomes regardless of antifibrinolytic treatment. Further, analysis of other large mostly single-center databases has not confirmed these findings.

At this time, a large prospectively randomized, double-blinded multicenter trial comparing aprotinin, TXA, and EACA in patients undergoing cardiac surgery was halted because of higher rates of adverse events in the aprotinin group. The details of this trial are pending. Nonetheless, in light of these recent developments and on the basis of other data reported from analysis of outcomes from a large administrative database, the U.S. Food and Drug Administration has requested a marketing suspension of aprotinin until the data can be reviewed.

After discussing all the options, the surgical team decided that TXA would be used for this procedure. The patient had an otherwise uneventful procedure receiving two saphenous vein bypass grafts to the circumflex and right coronary arteries. The duration of CPB was 36 minutes, and aortic cross-clamp time was 58 minutes. Heparin was adequately reversed with protamine with a final ACT of 121 seconds. After ample surgical hemostasis was achieved, the sternum was closed, and the patient was brought to the cardiac surgical intensive care unit. Chest tube output was closely monitored for 24 hours with only minimal drainage. The patient was discharged home on postoperative day 5 following an uncomplicated recovery.

#### KEY MESSAGES

1. The main pharmacologic treatment for preventing excessive bleeding during cardiac surgery is antifibrinolytic drugs such as TXA, EACA, and aprotinin.
2. Lysine analogs inhibit the process of fibrinolysis by adhering to the lysine-binding site on plasminogen.
3. Aprotinin is a serine protease inhibitor inhibiting several important enzymes including plasmin and kallikrein.
4. The safety of aprotinin was recently questioned in a recent retrospective data analysis obtained in a multicenter study. This analysis suggested that patients receiving aprotinin during cardiac surgery had a higher risk for myocardial infarction, stroke, renal dysfunction, and death compared with lysine analog antifibrinolytics.

## QUESTIONS

1. What is the incidence of reoperation in cardiac surgery?

Answer: Resternotomy for postoperative bleeding is required in approximately 3% to 6% of cardiac surgical patients.

2. What is the principal mechanism of action of EACA?

Answer: EACA is a synthetic derivative of the amino acid lysine. Lysine analogs inhibit the process of fibrinolysis by adhering to the lysine binding site on plasminogen.

3. Is aprotinin nephrotoxic?

Answer: Aprotinin use is associated with transient increase in serum creatinine levels that might reflect its effect on the proximal renal tubules.

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# The Use of Recombinant Factor VIIa in Cardiac Surgery

Jay K. Levin

## **CASE** FORMAT: REFLECTION

A 73-year-old female presented for aortic and mitral valve replacement surgery. Over the previous 6 months, she had noticed increasing dyspnea with activity and occasional chest pain. Preoperative echocardiography demonstrated severe aortic stenosis and moderate-to-severe mitral regurgitation. Ten years previously, she had undergone uncomplicated coronary bypass grafting. Recent coronary angiography demonstrated that her bypass grafts were patent and that no new significant coronary artery stenosis had developed. After an otherwise uncomplicated operation and separation from cardiopulmonary bypass (CPB), significant bleeding occurred despite having achieved her baseline-activated clotting time by protamine administration. No obvious cause of surgical bleeding was evident. Although the patient remained hemodynamically stable, blood drained continuously from the chest tube even after administering four units of fresh frozen plasma. The anesthesiologist considered administration of recombinant factor VIIa (rFVIIa).

## **DISCUSSION**

Often multifactorial, postbypass coagulopathy presents a challenge in managing cardiac surgical patients especially after “re-do surgery” (with repeat sternotomy) or prolonged CPB.<sup>1</sup> Causative factors include preoperative antiplatelet therapy, residual heparin effect, hypothermia, a relative and absolute decrease in platelet number and function, fibrinolysis, and a decrease in coagulation factors and function.

### **What is the initial management of post-CPB bleeding?**

Management of excessive bleeding after CPB requires an evaluation of the cause(s) including those of surgical origin. Immediate responses include management of hypothermia and/or administration of additional protamine as indicated (by temperature and activated clotting time measurement, respectively). Estimation of platelet count and performing coagulation studies are indicated. On-site coagulation testing such as thromboelastography provides a relatively fast and reliable, but non-specific, assessment of coagulation status including coagulation factor deficiency, platelet dysfunction, and fibrinolysis.

## **Mechanism of Action of rFVIIa**

In 1988, rFVIIa was administered to a patient with hemophilia A undergoing synovectomy.<sup>2</sup> Patients with hemophilia exposed to allogenic blood factors often have inhibitory antibodies to coagulation factors VIII and IX, limiting their effectiveness in the treatment of acute hemorrhage. FVIIa combines with tissue factor released by injured cells and initiates fibrin formation by activating factors IX and X.<sup>3</sup> When administered in doses that achieve supraphysiologic concentrations, rFVIIa can increase thrombin synthesis directly, and the resulting products are particularly resistant to degradation by plasmin.<sup>4</sup>

## **What are the Indications for rFVIIa?**

The current approved indications for administering rFVIIa include the treatment of bleeding in hemophiliac patients with inhibitors to factor VIII, congenital factor VII deficiency, and Glanzmann’s thrombasthenia. rFVIIa has been used off-label for excessive nonsurgical bleeding after trauma, liver resection and transplant, prostatectomy, intra-abdominal hemorrhage, intracerebral hemorrhage, and cardiac surgery.

### **Off-label administration of rFVIIa to cardiac surgical patients?**

The widespread administration of rFVIIa to patients undergoing cardiac surgery<sup>5–10</sup> is based on early case reports showing remarkable reduction in bleeding after CPB following complicated coronary artery bypass grafting, ventricular assist device placement, and repeat sternotomy. One case report described the use of rFVIIa to reverse lepirudin anticoagulation following CPB for a patient with a history of heparin-induced thrombocytopenia. Another case report described administration of rFVIIa following CPB in a patient with a history of anaphylactic reaction to protamine. Several retrospective studies have shown rFVIIa to be efficacious in managing refractory bleeding post-CPB, decreasing blood loss, normalizing coagulation factors, and decreasing the need for further blood product administration. One case series showed an immediate decrease in postoperative bleeding but no change in the volume of allogenic blood transfused during the first 24 hours postoperatively.

The currently available prospective, randomized, placebo-controlled trials of rFVIIa after cardiac surgery are limited by small numbers of patients studied. In a study of 10 patients undergoing complex cardiac surgery with CPB, the use of rFVIIa was shown to decrease transfusion of allogenic blood products and a tendency toward reduced blood loss. Aprotinin

was administered to both groups of patients. In a study evaluating pediatric cardiac surgical patients, rFVIIa failed to decrease blood loss or transfusion requirements. Thus, a large prospective, randomized, placebo-controlled trial examining the efficacy of rFVIIa to decrease bleeding and blood transfusion after cardiac surgery is needed.

The optimal dose of rFVIIa to decrease bleeding while not increasing the risk of adverse events is yet to be elucidated. Reported doses range from 25 to 195  $\mu\text{g}/\text{kg}$  (90  $\mu\text{g}/\text{kg}$  is used most commonly). rFVIIa, 40  $\mu\text{g}/\text{kg}$ , was successful in stabilizing uncontrolled bleeding after cardiac surgery.<sup>8</sup> A dose-finding study for rFVIIa in this setting is also required.

### Risk of Thromboembolic Events

Prothrombotic adverse effects are the major concern with the use of rFVIIa. In low concentrations, rFVIIa activates thrombin formation at sites of tissue factor exposure. At greater concentrations, generated thrombin can diffuse from the sites of vascular injury and could initiate intravascular thrombosis. Normally, naturally occurring anticoagulant proteins such as antithrombin III inactivate excessive thrombin formation. After acute illness or surgery with CPB, however, antithrombin III concentrations are decreased, predisposing to intravascular thrombosis.

Several of the retrospective studies and prospective, randomized, blinded, placebo-controlled studies that reported on the efficacy of rFVIIa for excessive bleeding after cardiac surgery reported safety end points, showing no increase in thromboembolic events. Two case reports (patients with hemophilia after lung transplantation) describe likely thrombotic events in patients receiving rFVIIa. Thus the safety of rFVIIa when used in the setting of perioperative bleeding has not been established.

#### KEY MESSAGES

1. Nonsurgical bleeding after cardiac surgery is usually multifactorial in origin.
2. When administered in doses that achieve supraphysiologic concentrations, rFVIIa increases thrombin synthesis directly.
3. Currently approved indications for rFVIIa include the treatment of bleeding in patients with hemophilia with inhibitors to factor VIII, congenital factor VII deficiency, and Glanzmann's thrombasthenia.
4. The safety of rFVIIa in the setting of perioperative bleeding has not been established.

### QUESTIONS

#### 1. What is the physiologic role of FVII in coagulation?

Answer: In its activated form, FVIIa combines with tissue factor released by injured cells and initiates fibrin formation by activating factors IX and X.

#### 2. What are the currently approved indications for administration of FVIIa?

Answer: Currently approved indications for rFVIIa include the treatment of bleeding in hemophilic patients with inhibitors to factor VIII, congenital factor VII deficiency, and Glanzmann's thrombasthenia.

#### 3. What dose of FVIIa might be administered to a patient bleeding excessively after cardiac surgery?

Answer: Reported doses range from 25 to 195  $\mu\text{g}/\text{kg}$ ; doses of 90  $\mu\text{g}/\text{kg}$  have been used most commonly.

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# Postoperative Neuropathy After Cardiac Surgery

Ioanna Apostolidou and Jason S. Johnson

## CASE FORMAT: REFLECTION

A 56-year-old, 112-kg, 170-cm male with three-vessel coronary artery disease, hypertension, and type 2 diabetes mellitus presented for coronary artery bypass grafting surgery. The patient's symptoms included chest pain with exertion that was relieved with rest. His current medications were metformin, lisinopril, and metoprolol. He was a nonsmoker, used alcohol socially, and was employed as a data analyst.

The patient's vital signs were as follows: temperature, 37.2°C; blood pressure, 142/86 mm Hg; heart rate, 64 beats per minute; and respiratory rate, 14 breaths per minute. Physical examination showed an obese male with clear bilateral breath sounds and a regular heart rate with no murmur. There was no carotid bruit.

Preoperative laboratory findings revealed normal chemistry, cholesterol, and blood cell counts. Preoperative electrocardiogram readings showed left ventricular hypertrophy but was otherwise normal. At stress exercise testing, significant ST depression occurred in the lateral leads, and subsequent coronary angiogram readings demonstrated 80% stenosis in the left anterior descending artery and 90% stenosis in the circumflex artery and right coronary artery. Ventricular function was normal as were valve anatomy and function.

After induction of anesthesia using etomidate, fentanyl, midazolam, and rocuronium, the patient's airway was secured with an endotracheal tube. A 20-gauge left radial arterial catheter was inserted. A pulmonary artery catheter was advanced in the pulmonary artery via a 9-F introducer sheath (multiaccess catheter) inserted in the right internal jugular vein under ultrasound guidance. The patient's arms were placed at his side in a neutral forearm position, and elbows, forearms, and hands were padded with foam pads. A balanced anesthesia technique was used for anesthesia maintenance with isoflurane, fentanyl, rocuronium, and midazolam.

The surgical technique entailed a median sternotomy with sternal retractors placed to facilitate left internal mammary artery dissection. Saphenous vein grafts were used for the remaining grafts. Total cardiopulmonary bypass time was 2 hours. The patient's heart function was restored without inotropic support, and separation from cardiopulmonary bypass was accomplished without difficulty. Intraoperative fluids consisted of one liter 5% albumin and three liters of Lactated Ringer's solution. The total operative time was 6 hours. The patient was brought to the intensive care unit and received a nitroglycerin infusion of 0.5 µg/kg per

minute, while mechanical ventilation was maintained. No intraoperative complications were noted, and the patient's trachea was extubated 4 hours after admission to the intensive care unit.

On the first postoperative day, the patient complained of right-hand numbness and grip strength weakness. Upon further evaluation, sensory loss was detected at the ulnar side of the wrist as well as the dorsal and palmar surfaces of the fifth and medial half of the fourth finger. The patient's hand had a claw-shaped appearance at rest. Tests of motor function showed weakness of flexion of the second to fifth fingers. The appearance of the elbow was normal. An ulnar neuropathy was diagnosed. A physical therapist was consulted to evaluate the patient. By the third postoperative day, the patient had approximately 50% return of strength to the hand but continued to have numbness.

On the fifth postoperative day, the patient was referred to the neurology service for further evaluation. Electromyography (EMG) was performed and showed a pattern consistent with long-standing carpal tunnel compression. On further questioning, the patient recalled occasional numbness in his hands after working long hours at the computer. Over the course of 3 months, the patient's symptoms returned to their preoperative level, with full recovery of hand motor function; he was referred to a hand specialist for treatment of his carpal tunnel disease.

## CASE DISCUSSION

### Perioperative Peripheral Nerve Injury

Although peripheral nerve injury (PNI) is not a life-threatening complication, it can bring significant distress to the patient and anesthesia provider and can result in short-term, or rarely in long-term, disability. Consequently, PNI poses a major risk for medical practice liability. Perioperative nerve damage was the second major injury (16%) from the ASA Closed Claims Database following death (32%). Ulnar neuropathy is the most frequent nerve injury (28%) followed by brachial plexus (20%), lumbosacral (16%), and spinal cord (13%) neuropathies.<sup>1,2</sup>

The mechanism of perioperative neuropathies is incompletely understood. Although improper patient positioning causing nerve compression, stretching, and ischemia, direct trauma or metabolic derangements can lead to nerve injuries, in the majority of the reported cases, patient positioning is

unrelated to the injury, and an explicit mechanism was not identified.<sup>3-5</sup>

PNI can present with sensory, motor, or mixed deficits of the area supplied by the affected nerve. Isolated sensory deficits are usually transient and typically resolve in days or weeks without any intervention. Motor deficits are more serious and the patient should be referred to a neurology department for further evaluation and management. Persistent sensory deficits lasting more than 5 days should also be referred to neurology.

Nerve conduction studies and EMG can help in defining the type of nerve injury (axonal, demyelination, or mixed), its distribution (proximal, distal, symmetric, asymmetric), and the severity and degree of motor or sensory involvement.<sup>6</sup>

### Peripheral Nerve Injuries Following Cardiac Surgery

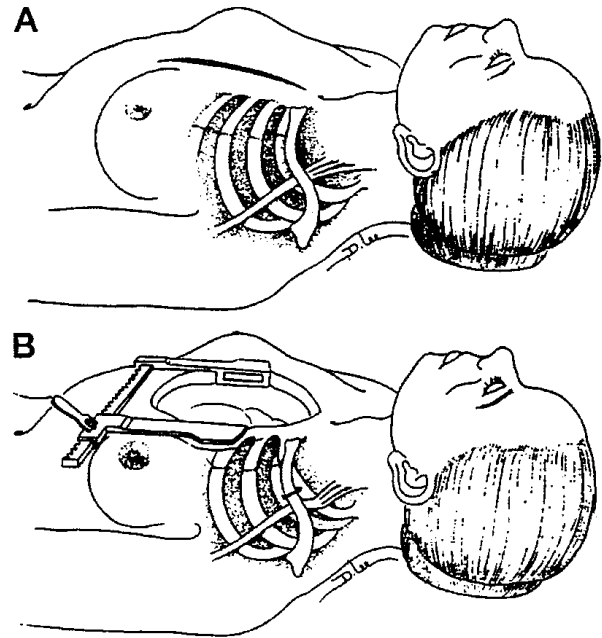
Various PNIs can be a complication of cardiac surgery.<sup>7,8</sup> Brachial plexus neuropathies, phrenic nerve injuries, saphenous neuropathy, recurrent laryngeal nerve injuries, sympathetic chain disturbance with resultant Horner's syndrome, and optic neuropathy have been described.

#### BRACHIAL PLEXUS

The frequency of brachial plexus injury is estimated at 2% to 18%. It is usually caused by stretching or trauma of the lower roots (C8-T1) resulting in ulnar neuropathy.<sup>9</sup> Excessive sternal opening and cephalad placement of the sternal retractor during sternotomy as well as asymmetric retraction during internal mammary artery dissection along with first rib fracture can cause compression and stretching of the brachial plexus (Fig. 8.1). More commonly, the plexus becomes stretched between a fixed position within its fascial plane and proximally fixed origins. Prolonged stretching of the plexus interferes with axonal transport and leads to transient neuropraxia. Somatosensory-evoked potential studies of the plexus demonstrated greater than 50% amplitude reduction after placement of sternal retractors.<sup>10</sup> Risk factors that may worsen the injury or lead to permanent symptoms include pre-existing neurologic injury such as cubital or carpal tunnel entrapment and advanced age. This scenario was described as the "double-crush" phenomenon in which two injuries to any single nerve will present with significant symptoms, whereas either injury by itself would be asymptomatic. Smoking, diabetes mellitus, height, and weight do not correlate well with risk. Male patients seem to be at a slightly greater risk than females to have permanent symptoms.<sup>7,8</sup> Symptoms vary with the location and severity of injury.

#### PHRENIC NERVE AND RECURRENT LARYNGEAL NERVE

Injury of the phrenic nerve and recurrent laryngeal nerve, respectively, are two well-known potential complications of cardiac surgery.<sup>11,12</sup> Topical hypothermia with ice slush and/or cardioplegia has been implicated as the principal cause. Sternal retraction, internal mammary artery harvesting, and central venous catheterization have been also related to nerve dysfunction. Unsuccessful attempts of transesophageal echocardiography probe placement have also been implicated in recurrent laryngeal nerve dysfunction. Phrenic neuropathy causing diaphragmatic dysfunction should be considered in



**Figure 8.1** • (A) Normal course of the brachial plexus as it passes over the first rib. (B) Opening the sternum widely causes superior rotation of the first rib that pushes the clavicles into the retroclavicular space leading to stretching of the brachial plexus. (Reproduced with permission from Graham JG, Pye IF, McQueen IN. Brachial plexus injury after median sternotomy. *Ann Thorac Surg* 1971;4:315-319.)

patients unable to be weaned from mechanical ventilation after cardiac surgery. Similarly, recurrent laryngeal nerve injury may result in postoperative respiratory failure from vocal cord dysfunction. Radiography, ultrasonography, and EMG are currently used diagnostic techniques.

#### SAPHENOUS NERVE

Saphenous neuralgia can result from harvesting the saphenous vein.<sup>13</sup> Endoscopic vein harvesting techniques may reduce incisional pain, but the benefits on saphenous neuralgia need to be further explored.

#### OPTIC NERVE

Ischemia of the optic nerve resulting in visual deficits is an infrequent but serious complication of cardiac surgery. Prolonged hypotension, emboli, hemorrhage, and anemia can decrease perfusion to any component of the optical pathway from the retina to the occipital lobe.<sup>2</sup>

### Central Venous Catheterization and Nerve Injury

Nerve injury is an infrequent complication of central venous cannulation (<1%). It is caused by direct nerve puncture or compression by a hematoma. Several cases of brachial plexus palsy, phrenic nerve, and recurrent laryngeal nerve injury have been reported after multiple attempts of internal jugular vein or subclavian vein catheterization. The use of ultrasound

to facilitate central venous cannulation may reduce the frequency of nerve injury by decreasing the number of venipuncture attempts. The clinical benefits of ultrasound-guided cannulation are greater success rate, fewer attempts, and a lower rate of complications (primarily arterial punctures) when compared with the landmark method.<sup>14</sup> Ultrasound use should be considered in difficult cases such as in patients with distorted anatomy, obesity, and scars at the cannulation site.

### Ulnar Neuropathy in Noncardiac Surgery

Ulnar neuropathy (UN) is the most frequent nerve injury reported in the ASA Closed Claims Database.<sup>1</sup> Compression injuries of the ulnar nerve result in immediate symptomatology; however, delayed onset of UN, usually 24 hours after surgery, supports a mechanism other than direct nerve compression as a primary cause in these cases.<sup>5,15</sup> The most common sites of injury are either at the elbow or higher in the brachial plexus course. UN can occur despite careful padding of the upper extremity. Risk factors associated with UN are male gender, body mass index extremes, and hospital stay duration. Symptoms of UN include sensory deficits in the ulnar and palmar aspect of the fifth and the medial half of the fourth digit, handgrip weakness, and fourth and fifth finger clawing from hand muscle imbalance. Pre-existing latent neuropathy conditions may predispose patients to a perioperative UN. This finding is supported by abnormal nerve conduction studies not only of the affected site but also of the contralateral site in a significant proportion of patients.

### Prognosis of Peripheral Neuropathies After Cardiac Surgery

The outcome of peripheral neuropathies depends on the type and severity of injury. Most common deficits are transient with complete recovery within 6 to 8 weeks. Rarely, symptoms persist for more than 4 months with slow improvement over time.<sup>7,8,16</sup>

### Prevention Strategies and Management of Perioperative Neuropathies

Preventing perioperative neuropathies is a very important part of perioperative care of all surgical patients. Proper patient positioning and padding to avoid direct compression or stretching of the peripheral nerve is of paramount importance especially for prolonged duration procedures. For the upper extremities, avoid pressure over the ulnar groove at the elbow and spiral groove of the humerus and avoid arm abduction greater than 90 degrees in a supine position. For the lower extremities, avoid overextension of the hamstring muscle and avoid pressure of the peroneal nerve at the fibula head. Place protective padding at the pressure nerve sites and use a chest roll in patients in the lateral decubitus position.<sup>17</sup> Peripheral nerve injuries identified in the postoperative period require prompt and thorough evaluation, complete documentation, and close monitoring. If symptoms are severe or persist beyond 1 week postoperatively, a neurologist should evaluate the patient. EMG studies may help to define the type and location of the nerve injury or may reveal a pre-existing condition.

### KEY MESSAGES

1. Brachial plexus injuries commonly occur during cardiovascular surgery.
2. All PNIs should be followed closely and referred for further evaluation as appropriate.
3. The majority of PNIs have a good overall prognosis with complete resolution of symptoms within weeks or months of the injury.
4. EMG can identify pre-existing neuropathies if performed early in the evaluation of a perioperative injury.

### QUESTIONS

1. Which neuropathies are most commonly encountered during the perioperative period?

Answer: UN is the most frequently encountered nerve injury (28%) followed by brachial plexus (20%), lumbosacral (16%), and spinal cord (13%) neuropathies.<sup>1,2</sup>

2. Which PNIs are associated with cardiac surgery?

Answer: Brachial plexus neuropathies, phrenic nerve injuries, saphenous neuropathy, recurrent laryngeal nerve injuries, sympathetic chain disturbance with resultant Horner's syndrome, and optic neuropathy have been described following cardiac surgery.

3. Which peripheral neuropathies are associated with central venous catheterization?

Answer: Cases of brachial plexus palsy, phrenic nerve, and recurrent laryngeal nerve injury have been reported after multiple attempts at internal jugular vein or subclavian vein catheterization.

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# Postoperative Visual Loss

Laurel E. Moore

## CASE FORMAT: REFLECTION

A 57-year-old male with a history of prior lumbar fusion presented for spinal fusion from T12-L4. The patient's past medical history was significant for moderate obesity (body mass index, 30 kg m<sup>2</sup>), type 2 diabetes, and well-controlled hypertension. The patient's physical activity was markedly limited by back pain, but recent cardiac testing revealed good left ventricular function and no evidence of myocardial ischemia. Preoperative laboratory data were within normal limits including a hematocrit level of 45%. The patient's preoperative vital signs included a blood pressure of 150/90 mm Hg, heart rate of 75 beats per minute, and oxygen saturation of 96% on room air.

The surgery was prolonged (8 hours) but without significant complications. Mean arterial pressure was maintained within 20% of baseline with the exception of one brief (10-minute) episode of hypotension (mean pressure <60 mm Hg) associated with significant bleeding. The patient's estimated blood loss was 3000 mL. The least recorded hematocrit level was 24%. Replacement fluids included four units packed red blood cells, 6000 mL crystalloid, and 500 mL hydroxyethyl starch. Shortly after extubation in the postanesthesia care unit, the patient complained that he could not see.

## CASE DISCUSSION

### Visual Loss After Spine Surgery

Postoperative visual loss (POVL) has historically been associated with cardiac surgery and more specifically, with cardiopulmonary bypass. The occurrence of POVL, although fortunately rare, appears to be increasing, particularly in patients undergoing spine surgery.<sup>1</sup> Although temporary postoperative visual changes can occur as a result of corneal abrasions or transient corneal edema from the prone position, true POVL in spine-injured patients has an incidence of 0.1% to 0.2%.<sup>1,2</sup> In 2006, the American Society of Anesthesiologists (ASA) published the findings from its POVL registry of 93 spine-injured patients<sup>1</sup> as well as a practice advisory for POVL for patients undergoing spine surgery.<sup>3</sup>

### Relevant Anatomy of the Optic Nerve and Retina

The optic nerve can be described in four segments: (a) the intracranial segment (optic chiasm to the optic canal within the

lesser sphenoid wing); (b) the intracanalicular segment (within the optic canal); (c) the posterior or intraorbital segment (optic foramen to the lamina cribrosa); and (d) the anterior or intraocular segment (from the lamina cribrosa to the optic disc). The lamina cribrosa is a perforated membrane overlying the posterior scleral foramen through which the optic nerve and central retinal artery and vein enter the eye.

The retina receives its blood supply from branches of the ophthalmic artery, which is the first branch of the intracranial internal carotid artery. Once the ophthalmic artery passes through the optic foramen, it branches into several vessels including the central retinal artery and a series of posterior ciliary arteries.<sup>4</sup> Both arterial systems are necessary for retinal function and as end vessels, there is the potential for watershed regions at risk for ischemia.<sup>5</sup> The intraorbital optic nerve is supplied by a pial plexus, which in turn, is supplied by branches of the central retinal artery and posterior ciliary arteries.<sup>6</sup> The most anterior portion of the optic nerve is supplied primarily by short posterior ciliary arteries and not the central retinal artery.<sup>5</sup> It is not clear that the blood supply to the optic nerve is autoregulated during episodes of increased intraocular pressure.<sup>7</sup>

### Mechanism of Injury

The causes of POVL are multiple and include cerebral cortical infarction, pituitary apoplexy, direct injuries to the eye and visual tracts, and ischemic injuries to the optic nerve and/or retina. The most common of these are ischemic injuries to the visual tracts, which fall into two primary categories: central retinal artery occlusion (CRAO) and ischemic optic neuropathy (ION). ION can be further subdivided into posterior ischemic retinopathy (PION: optic nerve injury posterior to the lamina cribrosa) and anterior ischemic retinopathy (AION: optic nerve injury anterior to the lamina cribrosa). Because of the increasing incidence of blindness following spine surgery, POVL and more specifically, PION have drawn the attention of treating physicians, researchers, and the lay public. CRAO and ION will be discussed separately.

### CRAO

CRAO generally presents with painless monocular visual loss following emergence from anesthesia. CRAO may be an important mechanism of POVL after cardiac surgery because of the risk of emboli to the central retinal artery (incidence as high as 4.5%<sup>8</sup>), although ION is also clearly a mechanism of POVL in this setting. It is less common than ION after spine surgery. On fundoscopic examination, patients classically demonstrate retinal pallor with a cherry-red spot at the macula. The pupillary light reflex is reduced or absent in the affected eye.

In terms of mechanism, CRAO can be embolic or effectively produced by increased intraocular pressure limiting perfusion pressure to the retina. Intraocular pressure has been shown to increase in patients in the prone position.<sup>9,10</sup> Perfusion pressure may be further reduced if the patient's orbit is compressed against a head holder (classically a horse-shoe head holder) or some other object, the so-called head rest syndrome. Patients may present with marked orbital edema and limited extraocular movements (to complete ophthalmoplegia), as perfusion to the entire orbit including surrounding tissues and extraocular muscles may be compromised.

In the ASA visual loss registry,<sup>1</sup> 10 of 93 POVL patients undergoing spine surgery were determined to have CRAO. In contrast to the 83 patients with ION, the patients with CRAO were less likely to have been pinned using a Mayfield head holder (all were on head rests), procedures were shorter, and there was less blood loss. Furthermore, no patients with CRAO had bilateral injuries unlike 66% of ION patients. Whereas visual loss from CRAO is generally felt to have a better chance of visual recovery than ION, in the ASA registry, there was no difference in outcome between patients with CRAO and ION.

## ION

Of the 131 reported cases of visual loss in the ASA POVL registry between 1999 and 2004, 93 (72%) were associated with spine surgery, and 83 (89% of all spine cases) were caused by ION.<sup>1</sup> Clearly, this number is increasing, but whether this is related to more complex surgical procedures, patient factors, or better recognition of POVL is unclear. In any case, ION is a devastating complication without clear etiology, making prevention a challenge for surgeons and anesthesiologists.

Patients with ION present with painless binocular or monocular visual loss, and the severity can range from a field cut to complete loss of light perception. The problem is generally recognized upon emergence from anesthesia but may be delayed for hours. Like CRAO, patients have a reduced or absent pupillary light reflex. External evidence of eye injury is generally absent. In patients with AION, the initial fundoscopic examination reveals an edematous disc, whereas with PION, the initial fundoscopic examination findings are generally normal. Over time, patients with both AION and PION will develop fundoscopic evidence of disc degeneration, and the likelihood of significant visual recovery is poor.

Although it appears easy to explain ION on the basis of vascular disease and reduced oxygen delivery to the optic nerve, the etiology is more complicated. There are reports of ION occurring in patients with normal intraoperative hematocrit levels and perfusion pressures.<sup>11</sup> There are also rare reports of children developing ION,<sup>12</sup> which would imply that there is a population of patients who may be at increased risk for ION based on the anatomy of the blood supply to the optic nerve or lack of autoregulation for this blood supply. In the ASA registry,<sup>1</sup> 66% of patients with ION had bilateral symptoms suggesting that the defect, whatever it is, is global in nature. Certainly, patients have suffered ION without evidence of ischemic injury to other vascular beds (kidney, heart), implying that the visual system may be particularly sensitive to changes in oxygen delivery.

A possible mechanism of ION is an orbital compartment syndrome in which the optic nerve is swollen as a result of

increased venous pressure (prone position) or potentially large-volume crystalloid infusion causing tissue edema. This then causes the nerve to be compressed within its sheath or as it enters the orbital fossa or the eye itself.

Limited evidence indicates an association between sildenafil and ION, most commonly in males<sup>13</sup> but also in children.<sup>14</sup> One reference recommends the cessation of sildenafil at least 1 week preoperatively.<sup>15</sup>

## Risk Factors for POVL

Although risk factors for atherosclerotic disease such as hypertension, diabetes, and smoking have been put forth as risk factors for POVL (and this certainly seems intuitive), the evidence is less clear. As stated previously, there are clearly certain individuals who for whatever reason are at risk for POVL, but preoperative identification of these individuals is currently not possible. Although intraoperative hypotension and anemia would also appear to place patients at risk for POVL, and these two factors are reported in multiple case reports, they are not necessarily supported by larger samplings. There are reports, however, of POVL improving postoperatively with blood transfusion in the case of anemia<sup>16</sup> and with increased blood pressure.<sup>17</sup>

The two factors that are consistently supported as risk factors for POVL in spine-injured patients include prolonged surgical procedures and large blood loss. In the ASA registry, these are defined as procedures lasting greater than 6 hours and a predicted blood loss of greater than 1 liter.<sup>1</sup> Of the 93 spine-injured patients with POVL, 94% of the procedures lasted 6 hours or longer. Similarly, 82% of POVL patients had an estimated blood loss of 1 liter or greater. It is interesting that despite the fact that women undergo more spinal procedures than men, 72% of cases in the registry were men.

## Avoidance of POVL

As the etiologies of POVL are poorly understood, it is impossible to avoid this complication. However, there are a few clear preventive measures that may be taken. First, check the eyes of prone patients on a regular basis, at least every 15 minutes, to ensure that they are clear of pressure of any kind. Particularly for patients on head rests (as opposed to pins), proper initial positioning does not guarantee against subsequent head movement during surgery, causing the orbit to come into contact with the head holder. Furthermore, to optimize retinal or optic nerve perfusion pressure, whenever possible, the head position should be neutral and at or slightly above the level of the heart. In some patients with severe kyphoscoliosis, this optimal positioning may be impossible because of the fixed position of the head on the thorax.

The ASA practice advisory<sup>3</sup> was developed by a small task force of anesthesiologists, spine surgeons (both orthopedic and neurosurgical), and neuro-ophthalmologists who evaluated current data and surveyed practicing anesthesiologists and spine surgeons. The advisory was published to aid in clinical decision making and was not intended to be a formal guideline or standard of practice. Despite this, their review of the subject was comprehensive, and suggestions for care of spine-injured patients were thoughtful. A summary of their suggestions is as follows:

1. Although there are preoperative medical conditions such as anemia, atherosclerotic disease, and obesity, which *may*

be associated with POVL, at present, these cannot be considered predisposing conditions.

2. Factors that place patients as high risk for POVL include prolonged procedures (greater than 6.5 hours) and procedures involving large blood loss (average 45% of estimated blood volume).
3. Although there was agreement among consultants and subspecialty physicians that deliberate hypotension should be avoided in high-risk patients (with or without well-controlled hypertension), there was a split opinion whether induced hypotension should be used in patients without chronic hypertension. In the end, there were inadequate data to recommend against the use of deliberate hypotension. The advisory does recommend continuous blood pressure measurement in high-risk patients.
4. Regarding minimal acceptable hemoglobin levels, again, there was significant variation in the opinions of consultants and subspecialty physicians. The average minimal acceptable hemoglobin level as stated by those surveyed was 9.4 g/dL. The task force could determine no lower limit for hemoglobin concentration that has clearly been associated with the development of POVL.
5. In patients with significant blood loss, it was advised that colloids should be used in conjunction with crystalloids.
6. Although there was a consensus among neuroanesthesiologists that the prolonged use of  $\alpha$ -agonists may reduce perfusion pressure to the optic nerve, there were inadequate data to formulate an advisory on this topic.
7. Staged surgical procedures should be considered in high-risk patients.
8. With regard to postoperative management of the patient with POVL, although all groups agree that there is no proven treatment for ION, they also agree that anemia should be treated, blood pressure increased, and oxygen administered. In patients suspected of having POVL, urgent ophthalmologic consultation should be obtained, and magnetic resonance imaging should be considered to rule out intracranial causes of blindness.
9. Preoperative discussion of POVL should be considered for patients at high risk (prolonged procedure, anticipated large blood loss).

## Management of POVL

The patient presented in this case had at least two risk factors for POVL: he underwent an 8-hour procedure in the prone position and lost approximately 50% of his blood volume. Whether his history of hypertension or diabetes contributed to his risk is unclear. There were also episodes of reduced blood pressure intraoperatively, but this association with POVL is unclear.

There is no proven treatment for POVL. However, several steps should be taken urgently for this patient including rapidly increasing his blood pressure to at least his baseline value and ensuring that his hemoglobin level is within a reasonable range (9.0 g/dL or greater). Ophthalmologic consultation should be obtained immediately, and a fundoscopic examination should be performed in an effort to evaluate what type of injury may be present. Magnetic resonance imaging scans should be obtained.

In conclusion, POVL is a devastating complication following spine surgery with an outcome that is generally poor. The

incidence of CRAO may be reduced with close attention to the orbit intraoperatively, but ION is more sinister in its etiology and thus more difficult to prevent. Information available to us is limited because of the very rare incidence of this complication, and single-institution prospective studies are essentially impossible. Furthermore, there is currently no animal model for POVL. Until more data on the mechanisms of POVL are available, staged procedures, obsessive attention to the eyes of prone patients, and frequent consideration of oxygen delivery to the optic nerve and retina are the best preventive measures available.

## KEY MESSAGES

1. The most common causes of POVL are ischemic injuries to the visual tracts, which fall into two primary categories: CRAO and ION.
2. In patients undergoing spine surgery, prolonged surgical procedures and large blood loss are risk factors for POVL.
3. Although the incidence of CRAO can be decreased with close attention to the orbit intraoperatively, ION is more sinister in its etiology and thus more difficult to prevent.

## QUESTIONS

1. What is the incidence of POVL in patients who have undergone spine surgery?

Answer: True POVL in spine-injured patients has an incidence of 0.1% to 0.2%.

2. What are the anatomic segments of the optic nerve?

Answer:

- a. The intracranial segment (optic chiasm to the optic canal within the lesser sphenoid wing)
- b. The intracanalicular segment (within the optic canal)
- c. The posterior or intraorbital segment (optic foramen to the lamina cribrosa)
- d. The anterior or intraocular segment (from the lamina cribrosa to the optic disc)

3. What are the likely mechanisms underlying POVL?

Answer: These include cerebral cortical infarction, pituitary apoplexy, direct injuries to the eye and visual tracts, and ischemic injuries to the optic nerve and/or retina.

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# Postoperative Cognitive Dysfunction

Charles W. Hogue

## CASE FORMAT: REFLECTION

A 75-year-old male had undergone an otherwise successful coronary artery bypass graft (CABG) surgery with aortic valve replacement 1 month prior to attendance at his postoperative clinic. His medical history included hypertension, non-insulin-dependent diabetes mellitus, and several episodes of congestive heart failure in the month before his surgery. He was married, had retired as a factory worker, and was physically active until the onset of his current illness. His recent cardiac operation included 140 minutes of cardiopulmonary bypass (CPB), transfusion of two units of packed red blood cells, 18 hours of hospitalization in the intensive care unit, and 7 days of total postoperative hospitalization. The patient had a 1-day episode of atrial fibrillation on postoperative day 2 that converted to sinus rhythm with intravenous amiodarone. During his clinic visit, his wife and daughter were concerned that he seemed forgetful since surgery and his ability to concentrate, such as for reading the newspaper, had noticeably declined.

His vital signs were as follows: temperature, 36.9°C; blood pressure, 155/70 mm Hg; heart rate, 68 beats per minute; and respiratory rate, 20 breaths per minute. The patient's physical examination was unremarkable, and his medications included aspirin, warfarin, amiodarone, and atorvastatin. Twelve-lead electrocardiogram readings showed sinus rhythm, and laboratory results were acceptable. Physical examination, including a comprehensive neurologic exam, was normal. The patient was oriented to person, place, and time. He could repeat 7 numbers after a delay of 5 minutes with mild difficulty. His sensorium appeared normal, but he did admit that he had not felt "himself" since surgery. The plan was to discontinue warfarin and amiodarone.

## CASE DISCUSSION

### Cerebral Complications of Cardiac Surgery

Clinically, perioperative cerebral injury has a range of manifestations that includes its most notable form, ischemic stroke. Perioperative stroke occurs in 1.5% to 5.2% of patients after cardiac surgery.<sup>1,2</sup> The range in reported incidences depends on the patient populations (e.g., patient age and risk status, types of procedures), diagnostic definitions, and the intensity

of clinical surveillance. Contemporary studies using sensitive brain magnetic resonance imaging with diffusion-weighted imaging report that as many as 45% of patients who have undergone cardiac surgery have new ischemic brain lesions that are often clinically undetected. Hemorrhagic stroke is unusual as a primary cause of cerebral injury after cardiac surgery.

### Postoperative Cognitive Dysfunction After Cardiac Surgery

Postoperative cognitive dysfunction is another manifestation of brain injury from cardiac surgery that may be less clinically obvious yet more frequent, affecting 20% to 30% of patients 1 month after surgery.<sup>1-3</sup> This form of brain injury is detected by administering a battery of psychometric tests typically before and after surgery. These tests evaluate a broad range of brain areas subserving attention, short- and long-term memory, visuomotor function, and other cognitive domains. In some instances, cognitive dysfunction may be noticed by family members who detect mild changes in the patient's personality, attention, memory, or even the perceptions that their family member "is not the same after surgery."

### MECHANISMS

It is generally believed that all forms of brain injury from cardiac surgery (i.e., stroke, delirium, and neurocognitive dysfunction) arise from a similar mechanism and that the ultimate manifestation depends on the extent and location of brain injury (e.g., global vs. regional, motor cortex vs. areas subserving cognition). This theory, however, is based on indirect data and has not been conclusively proven. In general, perioperative brain injury results from cerebral embolism or cerebral hypoperfusion that is exacerbated by inflammatory processes induced by CPB and/or ischemia-reperfusion injury. Abnormal endothelial functions resulting from ischemic damage and inflammatory processes leading to impaired microcirculatory flow likely contribute to subsequent injury. Cerebral emboli are often arbitrarily classified as macro- and microembolism. Examples of the former include atheroembolism arising from an atherosclerotic ascending aorta. The important role of atherosclerosis of the ascending aorta in brain injury has led to the practice of epiaortic ultrasound scanning before surgical manipulations of the aorta.<sup>1</sup> This method is more sensitive than palpation and transesophageal echocardiography for identifying aortic atheroma allowing the surgeon to choose alternate sites for cannulations and cross clamping. When atherosclerosis is severe, alternate surgical plans (e.g., different site of cannulation, off-pump surgery, etc.) may be necessary. There are many sources of microemboli including air entrained into the circulation or the

CPB circuit, particulate material arising from the operative field, microthrombus, and lipid emboli. The latter are believed to arise from pericardial fat that is aspirated with cardiomy suction during CABG surgery and then returned to the CPB reservoir unfiltered. Some centers advocate first processing shed pericardial blood with a cell saver before returning the blood to the CPB reservoir. The latter method was found to reduce the frequency of postoperative neurocognitive dysfunction in one study but not confirmed in another.

## RISK FACTORS

Some risk factors for stroke and postoperative neurocognitive dysfunction overlap, yet others are distinct. Patient age, atherosclerosis of the ascending aorta, prior stroke, diabetes, hypertension, peripheral vascular disease, duration of CPB, and postoperative atrial fibrillation are common risk factors for stroke and postoperative neurocognitive dysfunction.<sup>1-3</sup> The patient's level of education is inversely related to risk for cognitive dysfunction. An explanation for this relationship is not clear, but higher levels of education might identify individuals who are more proficient at taking psychometric tests or those with more cerebral reserve and are thus capable of tolerating an acute insult to the brain. Genetic susceptibility has been further identified to be associated with cerebral complications from cardiac surgery, but genotypes associated with stroke and neurocognitive dysfunction appear distinct.<sup>1</sup> Candidate genes include those associated with inflammatory cytokines and neuronal reparative pathways. It is hypothesized that abnormal secretion of inflammatory mediators during and after surgery or defective neuronal reparative processes might promote susceptibility to brain injury. Several prospectively randomized trials have reported that there is no difference in the frequency of cerebral outcomes between patients undergoing CABG surgery with or without CPB (off-pump surgery).<sup>1</sup> Other factors found to be associated with cerebral injury include cerebral hyperthermia caused by excessive rewarming after hypothermic CPB and low nadir hematocrit during CPB (<21% to 24%). Although hyperglycemia is implicated as worsening cerebral injury, there is no evidence to date that aggressive insulin treatment during surgery leads to a lower rate of stroke, encephalopathy, or neurocognitive dysfunction.

Methodologic limitations to psychometric testing include test-retest or practice effect whereby individuals undergoing psychometric testing score higher on repeated testing because of familiarization with testing methodology.<sup>4,5</sup> The statistical approach for defining cognitive decline varies between studies, and the approach chosen affects the ultimate frequency of the complications. There is no accepted standard for defining neurocognitive dysfunction. The often-used definition of a 20% decline in two or more psychometric tests after surgery from baseline has been challenged on the basis that there is often correlation between the results of many psychometric tests. Thus, if two test results are correlated, decrements on these tests might identify the same cognitive defect rather than distinct areas of dysfunction. Principal component analysis in which tests that correlate are grouped into general domains, and cognitive decline defined as a standard deviation decline from baseline overcomes this limitation.

Perhaps a larger limitation of psychometric testing as a means for detecting brain injury from cardiac surgery is its insensitivity and nonspecificity in an aging surgical population.<sup>4</sup> Many patients might have pre-existing cognitive deficits before

surgery such that they are incapable of further decrements of a magnitude necessary to show a standard deviation decline. This "basement effect" might overlook cognitive decrements that have profound importance to an elderly patient already functioning at a low cognitive level. At the same time, factors other than brain injury per se might lead to a false-positive diagnosis of neurocognitive dysfunction. Depression, pain, and chronic illness might all lead to low psychometric test results in the absence of cerebral injury during surgery.<sup>7</sup>

## ASSOCIATED OUTCOMES

Perioperative cerebral complications are an important source of patient morbidity and mortality. The chance of operative death for patients suffering a new stroke is greater than 10-fold higher than for patients who have not suffered a stroke (>20% vs. ~1% to 2%).<sup>1-3</sup> Stroke, after cardiac surgery is, in fact, the second most common cause of operative death after left ventricular failure. Cerebral complications are further linked to high hospital costs, admission to a secondary health care facility after surgery, high hospital readmission rates, and impaired quality of life.

The prognosis for patients with postoperative neurocognitive dysfunction has now been examined in several longitudinal studies. In a seminal investigation, investigators from Duke University found that neurocognitive dysfunction after CABG surgery predicted further cognitive decrement over a 5-year period.<sup>5</sup> Subsequent study by a team from Johns Hopkins University compared long-term cognitive function in patients recovering from CABG surgery with that of control subjects with coronary artery disease who were medically managed (plus/minus percutaneous coronary artery intervention).<sup>6</sup> These investigators found that the rates of long-term cognitive decline were no different in CABG surgical patients than controls over a 3-year period. These investigators are now reporting similar results after a 6-year follow-up period. The emerging data suggest that many patients with neurocognitive dysfunction after CABG surgery recover after 3 to 6 months. Further cognitive decline appears more related to the natural progression of cerebrovascular disease than the cardiac surgical procedure.

## DELIRIUM

Postoperative delirium (as distinguished from emergence delirium) is a disturbance of consciousness or awareness of the environment accompanied by a decreased ability to focus, sustain, or shift attention. Other features may include decrement in cognition (disorientation, reduced memory) or a perceptual disturbance (delusions or hallucinations) that is not caused by pre-existing dementia. Delirium is acute in onset developing over hours to days, and the course may fluctuate throughout the day. Delirium can be categorized into hypoactive, hyperactive, or mixed forms. Hypoactive delirium might be mistaken for depression or dementia. The frequency of delirium depends on the definitions, patient population, and type of surgery. Reported incidences after cardiac surgery range from 20% to 65% of patients and after hip surgery, 16% to 65%, particularly elderly patients and those undergoing CPB.<sup>8</sup> Delirium may be transient, or it may be associated with longer-term decrements in cognition, long-term disability, mortality, loss of independence, admission to a nursing home, and high health resource utilization. The etiology of delirium is unknown, but it may involve similar factors as those leading to postoperative neurocognitive dysfunction. Other factors implicated to be asso-

ciated with the condition include perioperative stress responses including systemic inflammatory response to surgery, abnormalities of brain cholinergic or norepinephrine neurotransmitter pathways, metabolic abnormalities, electrolyte abnormality, cerebral edema, hypoxia, or infections. Pre-existing patient factors, pain, and medications (e.g., benzodiazepines, drugs with central anticholinergic effects, corticosteroids, and some antibiotics) are suggested to increase susceptibility to postoperative delirium.<sup>8</sup> Acute or chronic substance abuse is further implicated. Data derived mostly from observational studies suggest a link between meperidine use in elderly patients and delirium. Although the data are presently insufficient, there currently does not appear to be an association among other analgesics and risk for delirium. Interventions that may improve or prevent delirium include frequently providing the patient with orientation cues such as a clock, calendar, and list of hospital staff. Physical exercise, visual aids, cognitive stimulation, regular daily routines, and sleep cycles are further measures.

### Postoperative Cognitive Dysfunction After Noncardiac Surgery

Cognitive dysfunction has been reported after noncardiac surgery mostly in elderly patients. Overall, the incidence in the immediate postoperative period might be as high as 25%, but this rate declines to roughly 10% by 3 months postoperatively.<sup>8,9</sup> The available evidence suggests that by 1 year, cognitive performance in most patients has returned to that expected for a matched control group not undergoing surgery. As with cardiac surgery, the detection of cognitive dysfunction after noncardiac surgery depends on baseline cognitive state and thus requires paired administration of a psychometric testing battery. Generalized cognitive tests such as the Mini-Mental Exam are mostly insensitive for detecting cognitive dysfunction. There is no signal test for this purpose, as a comprehensive battery is necessary to fully assess the broad range of cognitive domains that might be affected by surgery. Of note, the type of anesthesia, regional versus general, does not seem to influence the incidence of postoperative neurocognitive dysfunction.

#### KEY MESSAGES

1. Perioperative stroke occurs in 1.5% to 5.2% of patients after cardiac surgery.
2. Postoperative cognitive dysfunction affects 20% to 30% of patients 1 month after cardiac surgery.
3. Patient age, atherosclerosis of the ascending aorta, prior stroke, diabetes, hypertension, peripheral vascular disease, duration of CPB, and postoperative atrial fibrillation, are common risk factors for stroke and postoperative neurocognitive dysfunction after cardiac surgery.
4. Operative death for patients suffering a new stroke is greater than 10-fold higher than for patients who have not suffered a stroke (>20% vs. ~1% to 2%).

## QUESTIONS

### 1. What is the incidence of POCD after noncardiac surgery?

Answer: After noncardiac surgery, the incidence of POCD in the immediate postoperative period may be as high as 25%, but this rate declines to roughly 10% by 3 months postoperatively.

### 2. What is delirium?

Answer: Delirium (as distinguished from emergence delirium) is a disturbance of consciousness or awareness of the environment accompanied by a decreased ability to focus, sustain, or shift attention. Other features may include decrement in cognition (disorientation, reduced memory) or a perceptual disturbance (delusions or hallucinations) that is not caused by pre-existing dementia.

### 3. How can postoperative cognitive function be formally assessed?

Answer: It can be assessed by administering a battery of psychometric tests typically before and after surgery. These tests evaluate a broad range of brain areas subserving attention, short- and long-term memory, visuospatial function, and other cognitive domains.

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# Perioperative Myocardial Infarction

Joshua D. Stearns

## **CASE** FORMAT: STEP BY STEP

A 74-year-old female presented for a right femoral-popliteal arterial bypass. Her medical history was significant for hypertension, peripheral vascular disease, an 80 pack-year history of tobacco use, and recently diagnosed diabetes mellitus. The patient had undergone a cholecystectomy 20 years previously under general anesthesia without incident. Her current medications included lisinopril, glyburide, oxycodone and acetaminophen, and daily aspirin. Preoperative electrocardiogram (ECG) readings revealed normal sinus rhythm at 72 beats per minute and left ventricular hypertrophy by voltage criteria. The patient's preoperative hemoglobin level was 12.5 mg/dL, and her serum creatinine level was 1.3 mg/dL. The planned anesthetic technique was general endotracheal anesthesia with propofol induction and maintenance with fentanyl, nitrous oxide, and isoflurane along with vecuronium for muscle relaxation. Invasive arterial monitoring was utilized.

Initially, the patient tolerated the procedure well without evidence of myocardial ischemia by ECG monitoring (leads II and V5 and ST-segment analysis). An hour and a half into the procedure, however, and following approximately 800 mL of blood loss, the patient's heart rate increased to 110 beats per minute and there was evidence of ST-segment elevation in ECG lead II. Multiple lead analysis showed ST-segment elevation in leads II, III, and aVF. The patient's blood pressure slowly decreased from 135/85 mm Hg to 90/60 mm Hg over several minutes.

### **What measures should be have been taken at this point to limit myocardial ischemia?**

The treatment of myocardial ischemia is aimed at improving the balance between myocardial oxygen ( $O_2$ ) supply versus demand. Nitrous oxide should have been discontinued, and the patient should have been administered 100%  $O_2$ . Her blood pressure should have been increased by intravascular volume replacement and by administering a vasoconstricting agent such as phenylephrine. Avoiding drugs with  $\beta$ -adrenergic effects (e.g., ephedrine, epinephrine, or norepinephrine) is advisable to prevent further tachycardia and increased myocardial  $O_2$  demand. A short-acting  $\beta$ -blocker (e.g., esmolol) should have been considered to lessen the patient's heart rate. The target heart rate should be close to the patient's baseline or the lowest rate that is hemodynamically tolerated. The patient's arterial blood gas, hemoglobin, and electrolytes should have been measured. In light of the preoperative hemoglobin level and the

amount of blood loss, it was likely that the patient would need a transfusion of packed red blood cells. If these initial measures did not lead to an increase in blood pressure, a reduction in heart rate, and resolution of the ST-segment changes, the patient may have been experiencing left ventricular dysfunction or cardiogenic shock secondary to myocardial ischemia.

### **What mechanism of myocardial ischemia was most likely in this patient?**

The etiology of perioperative myocardial ischemia is often multifactorial. In this patient's situation, the presence of tachycardia, blood loss, and likely reduced hemoglobin concentration, suggests that the underlying mechanism for myocardial ischemia was myocardial  $O_2$  supply/demand mismatch. Hypovolemia leads to reflex tachycardia increasing myocardial  $O_2$  demand. At the same time, lessened blood  $O_2$  carrying capacity from reduced hemoglobin compromises myocardial  $O_2$  supply. Hypotension in this case might have resulted from reduced cardiac preload or reduced stroke volume from myocardial ischemia.

### **What other mechanisms are implicated in perioperative myocardial ischemia/infarction?**

Many episodes of myocardial ischemia occur despite a normal heart rate and blood pressure. The latter episodes result from reduced coronary artery blood flow often caused by a ruptured atherosclerotic plaque leading to platelet activation and release of vasoactive substances, thrombus formation, and partial or complete arterial obstruction. Atherosclerotic plaque disruption can occur in patients with only modest angiographic evidence for coronary artery stenosis. Furthermore, a stable coronary artery plaque can acutely transform to a plaque that is vulnerable to fissuring or frank rupture caused by localized inflammation or shear stresses resulting from sympathetic activation or rheologic factors. Patients with extant coronary plaque may be at additional risk for acute coronary syndromes as a result of the multiple stresses associated with surgery.<sup>1</sup>

### **What is the definition of myocardial infarction?**

The World Health Organization uses the following criteria for diagnosis of a myocardial infarction (MI). Two of the following must be present: (a) typical ischemic chest pain; (b) elevated serum creatine kinase (CK-MB enzyme); and/or (c) typical ECG findings including the development or presence of pathologic Q waves.<sup>1</sup>

In 2000, however, the European Society of Cardiology and the American College of Cardiology (ACC) revised the formal definition of an MI incorporating the use of increasingly

sensitive biochemical assays such as troponin I and T for the diagnosis (information to follow).<sup>2</sup>

### Do perioperative MIs present in a fashion consistent with the World Health Organization's definition of MI?

Most often, perioperative MI is not accompanied by typical chest pain caused by residual anesthetics, analgesic drugs, or sedation, especially in the setting of patients who remain intubated postoperatively. In addition, perioperative MI often manifests few of the classic ECG findings such as ST-segment elevation or Q waves.<sup>1</sup> As a result, the use of biochemical markers of myocardial injury often provides the most definitive diagnosis of perioperative MI. According to one study, 12% of patients developed elevated cardiac troponin T (cTnT) levels, while only 3% exhibited characteristics that confirmed perioperative MI by the World Health Organization definition.<sup>3</sup>

### Which biochemical markers are commonly used in the diagnosis of perioperative MI?

Biochemical markers for detecting myocardial injury include serum creatine kinase (CK-MB) and cTnT or troponin I (cTnI) assays. Cardiac troponins are both specific and sensitive for detecting myocardial injury and appear to provide improved detection of MI as compared to CK-MB levels.

### What threshold levels of CK-MB and cardiac troponins are diagnostic of perioperative MI?

CK-MB is not specific for cardiac tissue; thus, interpreting elevations in this isoenzyme is confounded perioperatively by other sources (e.g., muscle injury). Cardiac troponins are specific for the heart, but they are also released because of myocardial is-

chemia that does not necessarily lead to actual myocyte necrosis. There is much debate, therefore, as to the specific cut-off values that can be used to define an MI in the perioperative setting. Several studies suggest that even small elevations of cardiac troponins in the perioperative period identify some myocardial injury.<sup>4</sup> These elevations and the accompanying myocardial injury may be implications for both short- and long-term mortality. Over time, the threshold values have decreased suggesting that there is an association between small troponin elevations and cardiac outcome. Laboratory cut-offs for diagnoses differ from institution to institution. An increase in CK-MB >10% (upper limit of normal = 170 IU), cTn-I >1.5 ng/mL, or cTn-T >0.1 ng/mL have been shown to be independent predictors of mortality from cardiac events at 1-year and 5-year follow-up for patients undergoing vascular surgery.<sup>4</sup>

### What are the pharmacologic treatment options for patients diagnosed with a perioperative MI?

Medical therapy for perioperative MI is directed based toward rectifying myocardial O<sub>2</sub> demand/supply mismatch. Myocardial O<sub>2</sub> demand is reduced by the judicious use of  $\beta$ -blockers while ensuring myocardial perfusion pressure. Certainly, the most well-studied and used pharmacologic preventive treatment for perioperative myocardial ischemia or perioperative MI is  $\beta$ -blocker therapy. Several studies have shown reduced adverse cardiac events for patients in the perioperative setting, especially in patients considered at high risk for coronary heart disease. Patients considered high risk include those with risk factors such as diabetes mellitus and hypertension as well as patients who have been shown to exhibit "inducible" myocardial ischemia by exercise or pharmacologic stress testing. (Table 11.1). Furthermore, the initiation of  $\beta$ -blockers days or weeks in advance of surgery appears to provide greater benefit (a target heart rate of <65 beats per minute is optimal).

**TABLE 11.1** ACC/AHA Recommendations for Perioperative Use of  $\beta$ -Blockers Based on Published Randomized Clinical Trials

Surgery	No clinical risk factors	One or more clinical risk factors	Coronary heart disease or high cardiac risk	Patients currently taking $\beta$ -blockers
<b>Vascular</b>	Class IIb, level of evidence = B	Class IIa, level of evidence = B	Patients found to have myocardial ischemia on preoperative testing: class I, level of evidence = B; patients without ischemia or not previous test: class IIa, level of evidence = B	Class I, level of evidence = B
<b>Intermediate risk</b>	Insufficient data	Class IIb, level of evidence = C	Class IIa, level of evidence = B	Class I, level of evidence = C
<b>Low risk</b>	Insufficient data	Insufficient data	Insufficient data	Class I, level of evidence = C

ACC, American College of Cardiology; AHA, American Heart Institute.

Adapted from Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Circulation* 2007;116:e418-499.

Aspirin has been shown to be beneficial in the setting of acute MI. Both its anti-inflammatory effects and antiplatelet aggregation effects appear to play a role in the reduction of thrombotic activity characteristic of the plaque rupture mechanism for MI. The benefits of aspirin may be increased in the perioperative setting because of the accompanying inflammatory response to surgery. A meta-analysis of perioperative use of aspirin identified an almost 50% reduction of postoperative acute MI when administered with a dose of 325 mg or less.<sup>5</sup> The relative benefits of aspirin (given via a gastric tube or rectally) for secondary prevention of myocardial injury will outweigh the minimal risk of enhanced bleeding for most surgical procedures.

Heparin has been a mainstay for the treatment of acute MI; however, in the postoperative setting, the advantages of unfractionated heparin, other anticoagulants (such as low-molecular-weight heparin or direct thrombin inhibitors such as bivalirudin), and antiplatelet drugs must be considered in reference to the risks of bleeding from the surgical wound. Antiplatelet drugs commonly used include clopidogrel and glycoprotein IIb/IIIa inhibitors.<sup>6</sup> The use of anticoagulants and/or antiplatelet drugs should be initiated with the consultation of a cardiologist. This consultation should address other potential therapies such as angiotensin-converting enzyme inhibitors might be further considered particularly for anterior MI or in the setting of left ventricular dysfunction. Increasing interest has been placed on the use of statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) in the prevention of MI. Their use in the acute setting of an MI is unclear, although initial data suggest that statins confer benefits when administered in the acute setting.

$\alpha$ -2 Adrenoceptor agonists such as clonidine and dexmedetomidine may have benefits if used prior to surgery; however, the slow onset of effect of  $\alpha$ -2 adrenoceptor agonists may limit their value in the treatment of an identified MI. Nitroglycerin use for coronary dilatation may be of benefit if hemodynamics are stable and if there is ongoing evidence by ECG of ischemia.<sup>7</sup>

### What potential interventions should be considered as treatment for ongoing ischemia or infarction?

Placement of an intra-aortic balloon pump should be considered for refractory or recalcitrant myocardial ischemia. The definitive treatment of an acute MI is coronary artery reperfusion. Thrombolytic therapy is contraindicated because of the recent surgical incision and may be less effective than percutaneous coronary artery interventions (PCI). Early consultation with an invasive cardiologist is mandatory when there is an acute MI. Prompt transfer of the patient to the coronary catheterization laboratory for coronary angiography and possible coronary artery angioplasty with or without stent placement may rescue compromised myocardium.<sup>7</sup>

### According to the ACC/American Heart Association Guidelines for Perioperative Cardiovascular Evaluation for Noncardiac Surgery, what would be an appropriate preoperative strategy for evaluating cardiovascular risk in the patient presented in this case?

The ACC/American Heart Association (AHA) Guidelines stratify perioperative cardiac risk and specify the appropriate

**TABLE 11.2** Cardiac Conditions That Should Have Further Evaluation in Advance of Surgical Procedure

1. Unstable coronary syndrome—unstable or severe angina
2. Decompensated congestive heart failure—NY class IV
3. Malignant arrhythmias including
  - i) High-grade atrioventricular block
    - a) Mobitz type II AV block
    - b) Third-degree AV block
  - ii) Supraventricular tachycardia
    - c) Atrial fibrillation with rapid ventricular response
    - d) Symptomatic bradycardia
    - e) Symptomatic ventricular arrhythmias
  - iii) New-onset ventricular tachycardia
4. Severe valvular disease
  - i) Severe aortic stenosis
  - ii) Severe mitral stenosis

Adapted from Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Circulation* 2007; 116:e418–499.

preoperative cardiac evaluation based on three components. First, active evidence of cardiac disease and/or of clinical risk factors helps determine proper cardiac evaluation (Tables 11.2 and 11.3). Patients demonstrating existing cardiac disease (major risk factors) should have further cardiac evaluation before surgery, whereas those presenting with clinical risk factors may or may not require further testing. Previous guidelines stratified clinical risk factors into mild-, intermediate-, and high-risk; however, the most recent ACC/AHA guidelines have replaced that stratification with a list of clinical risk factors (Table 11.3). Second, an evaluation of a patient's functional capacity is considered. Third, the type of surgery is factored into the algorithm with high- (e.g., vascular), intermediate-, and low-risk being assigned to each surgery (Table 11.4). According to the latest update, the presented patient had one clinical risk factor (diabetes mellitus) and was undergoing a high-risk procedure (vascular surgery). The case described does not, however, describe the patient's functional capacity. Nevertheless, the algorithm offers the practitioner the option of considering further cardiac evaluation or proceeding with the case using perioperative  $\beta$ -blockers.<sup>8</sup>

### What role does preoperative coronary revascularization play in the reduction of perioperative MI?

#### PCI

PCI includes both coronary angioplasty with or without the use of intraluminal stents. The routine use of these interven-

**TABLE 11.3** Clinical Risk Factors for Perioperative Cardiac Events

1. History of ischemic cardiac disease
2. History of compensated or previous heart failure
3. History of cerebrovascular disease
4. Diabetes mellitus
5. Renal insufficiency

Adapted from Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Circulation* 2007; 116:e418–499.

tions in advance of an elective surgery is heavily debated. To date, no randomized trials to evaluate the efficacy of preoperative percutaneous transluminal coronary angioplasty for reducing perioperative MI have been conducted. Several retrospective cohort studies have examined patient populations who underwent percutaneous transluminal coronary angioplasty in an effort to ameliorate symptomatic angina and/or to reduce perioperative risk of myocardial ischemia. Overall, the three studies reported a low incidence of perioperative MI and/or perioperative cardiac death.<sup>9–11</sup> Unfortunately, no comparison groups were analyzed.

The placement of coronary artery stents, either bare metal or drug eluting, prior to surgery introduces the need for antiplatelet drug therapy with aspirin and clopidogrel to avoid intrastent thrombosis. The optimum duration of dual antiplatelet drug therapy after PCI with intracoronary stent

placement is currently under debate. However, a widely used antithrombotic strategy should include the use of clopidogrel for 6 weeks with concomitant aspirin that should be continued for life. Stent manufacturers recommend that clopidogrel should be continued for at least 3 months with sirolimus-eluting stents and 6 months with paclitaxel-eluting stents.<sup>12</sup> Despite these recommendations, more recent experience suggests that dual antiplatelet therapy is needed for longer than 1 year after insertion of a drug-eluting stent. Elective surgery should be delayed if the patient has not received an adequate duration of dual antiplatelet drug therapy. The optimum management of patients requiring surgery during the window of mandatory dual antiplatelet drug therapy is not known. Consultation with a cardiologist should be made, and consider glycoprotein IIb/IIIa drug use while clopidogrel is stopped. Because of this management dilemma, the prophylactic use of PCI with stents as a strategy to reduce cardiac risk in the perioperative period is not well supported by the literature. If PCI with stenting has taken place in advance of surgery, an interval of at least 6 weeks should take place before surgery. In the case of drug-eluting stents, a minimum of 12 months should be considered<sup>8</sup> (Fig. 11.1).

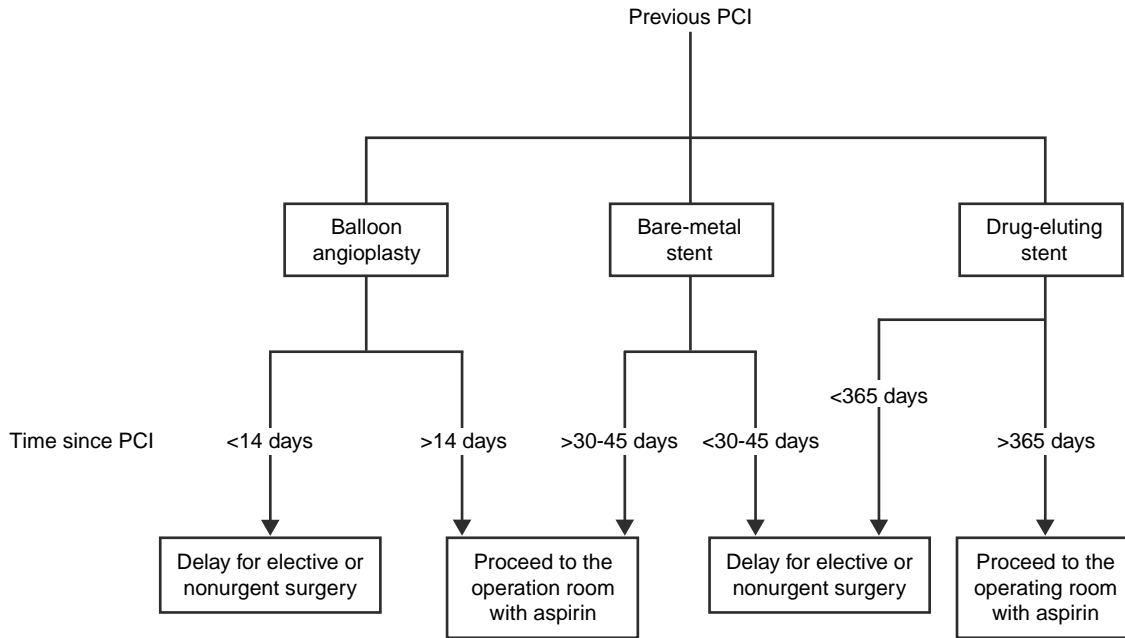
### Surgical Coronary Revascularization

Revascularization by coronary artery bypass grafting has been proposed and used as a means to reduce cardiovascular risk in high-risk patients undergoing noncardiac surgery. However, the Coronary Artery Revascularization Prophylaxis trial demonstrated that coronary artery revascularization prior to elective vascular surgery conferred no long-term outcome benefits.<sup>13</sup> As such, the decision to use coronary revascularization before elective surgery should be based on the same criteria for the use of coronary artery bypass grafting in patients not scheduled to undergo noncardiac surgery.

**TABLE 11.4** Cardiac Risk Stratification Based on Type of Surgery

Risk Stratification (Risk of Cardiac Events)	Types of Procedures
Vascular (>5%)	Aortic and other major vascular surgery Peripheral vascular surgery
Intermediate risk (1% to 5%)	Intraperitoneal and intrathoracic surgery Carotid endarterectomy Head and neck surgery Orthopedic surgery Prostate surgery
Low risk (<1%)	Endoscopic procedures Superficial procedures Cataract surgery Breast surgery Ambulatory surgery

Adapted from Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Circulation* 2007; 116:e418–499.



**Figure 11.1 • ACC/AHA Proposed Guidelines, Based on Expert Opinion, for Management of Patients with Recent Percutaneous Coronary Interventions Requiring Noncardiac Surgery.**

(Reproduced with permission from Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery]. *Circulation* 2007;116:e418–499.)

## KEY MESSAGES

1. Perioperative MI leads to significant morbidity and mortality and costs the health care system billions of dollars each year.
2. Perioperative MI is proposed to have two basic yet often overlapping mechanisms: (a) myocardial O<sub>2</sub> supply/demand mismatch and (b) ruptured coronary plaque or associated thrombus leading to coronary occlusion.
3. Perioperative MI is most commonly diagnosed by the presence of elevated cardiac enzymes because the usual cardiac symptoms are typically masked by anesthetic and analgesic drugs and also because it frequently occurs with few or none of the classic ECG findings.
4. Perioperative  $\beta$ -blocker use has been shown to be the most effective medical therapy for reducing perioperative MI—especially in high-risk patients, including those undergoing vascular surgery.
5. Perioperative use of aspirin and statin drugs may also reduce the risk of PMI.

## QUESTIONS

1. Which biochemical markers are commonly used in the diagnosis of perioperative MI?

Answer: Biochemical markers for detecting myocardial injury include CK-MB and cTnT or troponin I (cTnI) assays. Cardiac troponins are both specific and sensitive for detecting myocardial injury and appear to provide improved detection of MI as compared to CK-MB levels.

2. What limitations apply to interpreting elevations in biomarkers of myocardial injury?

Answer: CK-MB is not specific for cardiac tissue; thus, interpreting elevations in this isoenzyme is confounded perioperatively by other sources (e.g., muscle injury). Cardiac troponins are specific for the heart, but they are also released because of myocardial ischemia that does not necessarily lead to actual myocyte necrosis.

3. Why is aspirin administration indicated in the setting of acute MI?

Answer: Both its anti-inflammatory effects and antiplatelet aggregation effects appear to play a role in the reduction of thrombotic activity characteristic of the plaque rupture mechanism for MI.



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# Heparin-Induced Thrombocytopenia

Roy Kan

## CASE FORMAT: STEP BY STEP

A 56-year-old woman with hypertension and hyperlipidemia presented to the emergency department with congestive heart failure. A cardiology evaluation revealed triple-vessel coronary artery disease with marked global left ventricular hypokinesia (left ventricular ejection fraction, 15%). The patient underwent urgent coronary artery bypass surgery during which intravenous (IV) heparin 30,000 U was administered for cardiopulmonary bypass (CPB). Her platelet count prior to surgery was 180,000/ $\mu\text{L}$ .

The patient continued to do poorly after coronary revascularization with low cardiac output despite large doses of dobutamine and milrinone. The patient underwent placement of a biventricular assist device on the next day, during which IV heparin was administered again. There was a progressive decline in platelet count from 98/ $\mu\text{L}$  prior to the biventricular assist device placement to 36/ $\mu\text{L}$  3 days later.

### What causes thrombocytopenia?

In general, the etiology of thrombocytopenia includes hemodilution from infusion of fluids or blood products, increased platelet destruction, or reduced platelet production by the bone marrow. Increased platelet destruction may result from nonimmune causes (e.g., sepsis, disseminated intravascular coagulation, or thrombotic thrombocytopenic purpura) or from immune causes (e.g., posttransfusion purpura or idiopathic thrombocytopenic purpura). Drugs that can lead to immune-mediated thrombocytopenia include heparin, quinine, quinidine, sulfa drugs, vancomycin, and others. Platelet production by the marrow may be affected by disease conditions (e.g., aplastic anemia, leukemia, myelodysplasia) or drugs (e.g., cytotoxic agents, alcohol).

Given the association with heparin use in this case, the diagnosis of heparin-induced thrombocytopenia (HIT) must be actively excluded.

Heparin therapy was discontinued and replaced with lepirudin. Laboratory testing for heparin platelet factor 4 (PF4) complex antibodies was positive for HIT.

### What is HIT?

HIT is classified into two types. HIT type I is also known as *nonimmune heparin-associated thrombocytopenia*. It is the more benign of the two forms of HIT characterized by a typ-

ical onset time of 4 days after heparin exposure, a platelet nadir of 100,000 to 150,000/ $\mu\text{L}$ , and a recovery time of 1 to 3 days with minimal complications. It has an estimated incidence of 5% to 30%. HIT type I is caused by platelet microaggregation and subsequent sequestration in the spleen. It is not associated with heparin-dependent antibodies. Heparin administration should be continued despite the low platelet count.

HIT type II is an immune-mediated syndrome caused by an antibody to the heparin-PF4 complex. It is a disorder initiated by an immunologic response to heparin exposure and is characterized by an absolute or relative thrombocytopenia that paradoxically increases the risk of thrombosis, leading to life-threatening complications.

An estimated 600,000 new cases of HIT type II occur in the United States every year with thromboembolic complications occurring in approximately 300,000 patients and death in approximately 90,000 patients. Health care costs from HIT type II complications in cardiac surgery alone are estimated to be approximately \$300 million USD.

### What is the pathophysiology of type II HIT?

The pathogenesis of HIT has been thoroughly reviewed. The administration of heparin in susceptible patients leads to heparin binding to PF4 on the platelet membrane. The formation of heparin-PF4 complexes changes the conformation of PF4 exposing epitopes that allow its recognition and binding by immunoglobulin G (IgG). The platelets, in turn, are activated by the Fc domain of the IgG. A positive feedback loop is created whereby activated platelets release microparticles that promote thrombin formation, which, in turn, fuels further platelet activation. Activated platelets also release PF4, which leads to immune complex production. The resultant thrombocytopenia and thrombin generation produces a prothrombotic state, which is exacerbated by the antibody-mediated endothelial injury and tissue factor production.

The Iceberg Model of HIT proposed by Warkentin suggests that thrombocytopenia and associated thrombosis only occurs in a small subset of patients with platelet-activating antiheparin/PF4 antibodies. It has been estimated that about 7% to 50% of heparin-treated patients generate heparin-PF4 HIT antibodies.<sup>2</sup> HIT antibodies circulate only temporarily, with a median half-life of 85 days by antigenic assay. These antibodies may be clinically significant because the presence and concentration, regardless of thrombocytopenia, are associated with increased morbidity or mortality in various clinical

settings, such as acute coronary syndromes, hemodialysis, and cardiovascular or orthopedic surgery.

Both unfractionated and low-molecular-weight heparin can cause type II HIT, but the risk is higher with the former, particularly when given intravenously or in high doses. The use of both porcine and bovine can result in type II HIT, but the risk is higher with the latter.

High-risk groups for type II HIT include orthopedic patients given postoperative heparin as well as cardiac transplant and neurosurgery patients (11% and 15%, respectively). Other risk factors for HIT include high-titer, IgG HIT antibodies and female gender.

### What are the clinical manifestations and complications of type II HIT?

Type II HIT has three clinical presentations: (a) latent phase in which antibodies are present without thrombocytopenia, (b) HIT whereby antibodies are present with thrombocytopenia, and (c) heparin-induced thrombocytopenia-thrombosis (HITT) in which antibodies are present with thrombocytopenia and thrombosis.

Of the patients who develop latent type II HIT with IgG seroconversion, 30% to 50% will develop thrombocytopenia. Of these patients, 30% to 80% will demonstrate isolated thrombotic events, of which 0.01% to 0.1% will experience multiple thromboses or white clot syndrome. Bleeding is rare despite the severity of the thrombocytopenia. Approximately 10% of patients with HIT and thrombosis require a limb amputation. The mortality rate is approximately 20% to 30%.

Platelet counts of 20,000 to 150,000/ $\mu\text{L}$  are seen typically 5 to 10 days after exposure to heparin. A fall in platelet count of more than 50% is considered to be diagnostic. In patients with elevated baseline platelet counts, a 50% or greater decrease without falling below a normal platelet level may be observed. The platelet counts usually return to normal levels in 5 to 10 days after heparin is stopped.

Rapid-onset HIT leads to reduced platelet counts within minutes to hours of heparin exposure. This tends to occur in patients with preformed heparin-PF4 antibodies from a previous heparin exposure within the prior 3 months. The platelet count should be determined immediately for comparison with a prebolus count.

HIT can sometimes present days to weeks after heparin has been stopped. This scenario, known as *delayed-onset HIT*, is less common than the more rapid presentations of HIT but should be considered if a recently hospitalized, heparin-treated patient presents with thrombosis.

Up to 50% of patients with isolated HIT (thrombocytopenia with no evidence of thrombosis) develop clinical evidence of thrombosis despite cessation of heparin within the first week if no alternative anticoagulant is started. Clinical thrombosis may manifest as:

1. Venous thrombosis (30% to 70%)
  - a. Deep vein thrombosis
  - b. Pulmonary embolism
  - c. Adrenal vein thrombosis, leading to adrenal necrosis
  - d. Cerebral sinus venous thrombosis
  - e. Venous limb gangrene

2. Arterial thrombosis (15% to 30%)
  - a. Limb artery thrombosis
  - b. Stroke
  - c. Myocardial infarction
3. Skin lesions at heparin injection site (10%)
  - a. Skin necrosis
  - b. Erythematous plaques
4. Acute reaction after IV bolus of heparin (10%)
5. Disseminated intravascular coagulation (10%)

### How is HIT diagnosed?

HIT should be suspected whenever the platelet count decreases by 50%, or when new thrombosis occurs 5 to 14 days after the start of heparin therapy. Routine platelet count monitoring, including a pre-heparin value, is recommended for most heparin-treated patients. For patients with suspected HIT, laboratory testing is recommended, but because of its high thrombotic risk, treatment for such patients should not be withheld while waiting for laboratory results. Clinical scoring systems may be used to estimate the probability of HIT. An example of such a scoring system is the “Four Ts” (for timing, thrombocytopenia, thrombosis, and other sequelae). A score of 0, 1, or 2 is assigned depending on the onset time and severity of thrombocytopenia, the presence of thrombotic manifestations, as well as the absence of other causes of thrombocytopenia. An overall score greater than 6 is highly suggestive for HIT.

Laboratory testing for HIT antibodies may be divided into antigenic and functional testing. Antigenic tests include enzyme-linked immunosorbent assay and rapid particle gel immunoassay that detect antibodies to heparin-PF4 complexes or complexes of PF4 and other polyanions. Commercial enzyme-linked immunosorbent assay, which detect IgG, IgM, and IgA, are sensitive for detecting antibodies but are not specific for HIT. Measurement of only IgG antibodies enhances clinical specificity, whereas antibody titer based on the optical density can be more informative. Higher-titer antibodies are associated with increased thrombotic risk. Antibody titers by gel particle immunoassay correlate with clinical likelihood scores in suspected HIT.

Functional tests include the  $^{14}\text{C}$ -serotonin release assay and the platelet aggregation test. The platelet aggregation test measures platelet aggregation resulting from IgG in the serum or plasma of an HIT patient given heparin. It has a high specificity of 90%, is simple to perform, and is widely available. However, the sensitivity of this test is poor, although this can be improved by using washed platelets. The serotonin release assay measures serotonin released from aggregated platelets from HIT. Although this test has high sensitivity and specificity, it requires the use of radioactive reagents and is technically demanding and time consuming to perform.

### What is the treatment for HIT?

When HIT is suspected, all forms of heparins should be immediately stopped while awaiting laboratory confirmation of the diagnosis. Avoid using “flush” solutions containing heparin including dialysate fluid and central venous or pulmonary catheters with heparin coatings. Low-molecular-weight heparins should be avoided because of possible cross-reaction with heparin-PF4 antibodies to exacerbate HIT.

Serial monitoring of platelet counts is mandatory as is vigilant monitoring for thrombotic manifestations of HIT. Prophylactic platelet transfusion is not recommended, as it may increase the risk of thrombosis.

Heparin should be avoided, if possible, for as long as heparin-PF4 antibody testing is positive, although a longer heparin-free period is often preferred because of the availability of safe, effective alternative anticoagulants and uncertainty regarding the risk of recurrence on heparin re-exposure. The British Committee for Standards in Hematology recommends the use of nonheparin anticoagulation for most patients requiring anticoagulation with previous HIT.

Alternative anticoagulant coverage is used to prevent thrombotic complications. However, warfarin should not be used as the initial, sole anticoagulant therapy because of its slow onset of action. In addition, the protein C and protein S deficiency induced by warfarin can cause microvascular thrombosis resulting in coumarin-induced venous limb gangrene. If warfarin has already been started when HIT is recognized, vitamin K should be given to reverse the effects of warfarin and to minimize the risk of warfarin-induced limb gangrene or skin necrosis. Warfarin may be introduced at a later stage when platelet levels have normalized and when overlapping alternative anticoagulants are at therapeutic levels. Parenteral and oral anticoagulants should overlap for at least 5 days, with a therapeutic international normalized ratio achieved for at least 2 days before the parenteral anticoagulant is stopped.

Given the time course for thrombotic risk in HIT, nonheparin anticoagulation should be maintained for at least 1 month with a longer duration warranted if HIT-associated thrombosis occurred. Available agents include direct thrombin inhibitors such as lepirudin, bivalirudin, or argatroban. Consideration is given to the pharmacokinetic profile and route of elimination of each agent (Table 12.1). There are no agents currently available to reverse the anticoagulant effects of direct thrombin inhibitors.

An alternative to the direct thrombin inhibitors is danaparoid, a glycosaminoglycan derived from porcine intestine

that has been used safely and effectively in critically ill patients with HIT. Fondaparinux is a novel anticoagulant that is modeled after the antithrombin-binding pentasaccharide region of heparin. It has anti-Xa and anti-IXa activity that does not cross-react with HIT antibodies. Although it is approved in the United States and elsewhere for prophylaxis and treatment of venous thromboembolism, the usefulness of fondaparinux for the treatment of type II HIT has not been established.

The usefulness of antiplatelet agents has not been established. Aspirin has only marginal therapeutic benefit because of its variable inhibition of platelet activation by HIT antibodies. Although the prostacyclin analog, iloprost, has been used to treat patients with type II HIT undergoing CPB surgery in combination with heparin, its use has been limited by severe hypotension. The role of ADP inhibitors such as ticlopidine and clopidogrel in the treatment of HIT has not been evaluated.

### **An emergency heart transplant was arranged for this patient. What are the drugs available for anticoagulation during cardiac transplant?**

For patients with current or previous HIT who require cardiac surgery, the surgery should be delayed, if possible, until heparin-PF4 antibodies are negative. In patients with acute HIT undergoing cardiac surgery, direct thrombin inhibition is preferred over heparin or danaparoid. Of the direct thrombin inhibitors available, bivalirudin is preferred over lepirudin, as the former is least organ dependent for its metabolism and is not associated with anaphylaxis from lepirudin re-exposure. Appropriate dosing of the direct thrombin inhibitors during cardiac surgery has not been established, however, and no direct thrombin inhibitor is approved for use in this setting.

The most appropriate method for anticoagulation monitoring during CPB when direct thrombin inhibitors are used is not clear. The activated clotting time is affected by many variables

**TABLE 12.1** Drugs for Nonheparin Anticoagulation

	<b>Lepirudin</b>	<b>Argatroban</b>	<b>Bivalirudin</b>	<b>Danaparoid</b>	<b>Fondaparinux</b>
<b>Drug type</b>	DTI	DTI	DTI	Heparinoid	FXa inhibitor
<b>Clearance</b>	Renal	Hepatic	Renal, Enzymic	Renal	Renal
<b>Half-life</b>	80 min	40 min	36 min	7 h	15 h
<b>Cross-reactivity with HIT antibodies</b>	No	No	No	Minimal	Negligible
<b>Monitoring</b>	ECT or aPTT	ACT or aPTT	ACT or aPTT	Anti-FXa	Not required
<b>Target aPTT</b>	1.5–2.5 baseline	1.5–3 baseline	1.5–2.5 baseline	NA	NA
<b>Effect on INR</b>	Yes	Yes	Yes	No	No
<b>Approved in HIT</b>	Yes	Yes	Yes (for PCI)	Yes (no in USA)	No

ACT, activated clotting time; aPTT, activated partial thromboplastin time; DTI, direct thrombin inhibitors; ECT, ecarin clotting time; INR, international normalized ratio; NA, not applicable; PCI, percutaneous coronary intervention.

in addition to thrombin inhibition, including hemodilution, thrombocytopenia, and hypothermia. The activated clotting time, thus, is a poor monitor of thrombin inhibition or the effectiveness of anticoagulation. Thromboelastography has been used to monitor both clot initiation and clot strength during cardiac surgery with direct thrombin inhibition. The ecarin clotting time has been used for monitoring lepirudin and bivalirudin during cardiac surgery, but this is not a commercially available test in the United States.

Cardiotomy suction blood should be processed in a cell saver that uses citrate and not heparin for anticoagulation. Care must be taken to administer additional bivalirudin into the CPB reservoir after separation from bypass to ensure anticoagulation while the blood is recirculated.

### KEY MESSAGES

1. An estimated 600,000 new cases of type II HIT occur in the United States every year with thromboembolic complications occurring in approximately 300,000 patients, and death in approximately 90,000 patients.
2. The administration of heparin in susceptible patients leads to heparin binding to PF4 on the platelet membrane. The formation of heparin-PF4 complexes changes the conformation of PF4 exposing epitopes that allow its recognition and binding by IgG.
3. Type II HIT has three clinical presentations: (a) latent phase in which antibodies are present without thrombocytopenia, (b) HIT whereby antibodies are present with thrombocytopenia, and (c) HITT in which antibodies are present with thrombocytopenia and thrombosis.
4. When alternative anticoagulant coverage is used to prevent thrombotic complications, warfarin should not be administered as the initial, sole anticoagulant therapy because of its slow onset of action.

## QUESTIONS

### 1. How is HIT classified?

Answer: HIT is classified into two types. Type I HIT, also known as *nonimmune heparin-associated thrombocytopenia* is caused by platelet microaggregation and subsequent sequestration in the spleen. Type II HIT is an immune-mediated syndrome caused by an antibody to the heparin-PF4 complex.

### 2. What are the clinical manifestations and complications of type II HIT?

Answer: Type II HIT has three clinical presentations: (a) latent phase in which antibodies are present without thrombocytopenia, (b) HIT whereby antibodies are present with thrombocytopenia, and (c) HITT in which antibodies are present with thrombocytopenia and thrombosis.

### 3. How is HIT antibody detected?

Answer: Laboratory testing for HIT antibody is classified as antigenic or functional testing. Antigenic tests include enzyme-linked immunosorbent assay and rapid particle gel immunoassay that detect antibodies to heparin-PF4 complexes or complexes of PF4 and other polyanions. Functional tests include the  $^{14}\text{C}$ -serotonin release assay and the platelet aggregation test.

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# Hypertonic Saline Resuscitation

David M. Rothenberg

## CASE FORMAT: REFLECTION

A 33-year-old male presented to the emergency department having sustained a closed head injury and blunt abdominal trauma following a motor vehicle collision. He had suffered loss of consciousness at the scene but was now awake and complaining of neck and abdominal pain. His past medical and surgical histories were unremarkable. He was taking no medications and had no known allergies. He denied alcohol, tobacco, or drug use. The patient's vital signs were as follows: blood pressure, 90/60 mm Hg; heart rate, 110 beats per minute; respiratory rate, 24 breaths per minute; and his temperature was 36.5°C.

On physical examination, the patient was oriented to person only, and a left sixth cranial nerve palsy was demonstrated. Posterior neck tenderness was elicited, the lungs were clear to auscultation, his abdomen was distended, rebound tenderness was present, and bowel sounds were diminished.

Following administration of 3 liters of normal saline (at the scene and in the emergency department), laboratory results were as follows: hemoglobin, 9.6 gm dL<sup>-1</sup>; white blood cell count, 13,000/mm<sup>3</sup>; Na<sup>+</sup>, 145 mEq/L; K<sup>+</sup>, 3.6 mEq/L; HCO<sub>3</sub><sup>-</sup>, 18 mEq/L; Cl<sup>-</sup>, 110 mEq/L; creatinine, 1.4 mg%; and blood urea nitrogen, 31 mg%. Abdominal paracentesis was positive for blood. A chest radiograph revealed possible free air under the diaphragm. The patient's computerized tomography (CT) scan of the head and neck demonstrated bilateral frontal lobe contusions with a moderate-sized right frontal parietal subdural hematoma (Fig. 13.1) but a normal cervical spine. A perforated cecum was seen on abdominal CT.

The patient underwent exploratory laparotomy, drainage of the subdural hematoma, and insertion of an external ventricular drain and intracranial pressure monitor. He received a total of 6 liters of intravenous normal saline, 500 mL of human albumin, and 2 units of packed red blood cells. Forty-eight hours later, he remained comatose, and the CT scan of his head revealed diffuse cerebral edema. On the third postoperative day, he developed oliguria and was noted to have intra-abdominal pressures of 35 mm Hg.

## CASE DISCUSSION

Intravascular volume resuscitation in the setting of traumatic head injury, polytrauma, and severe burns is controversial not

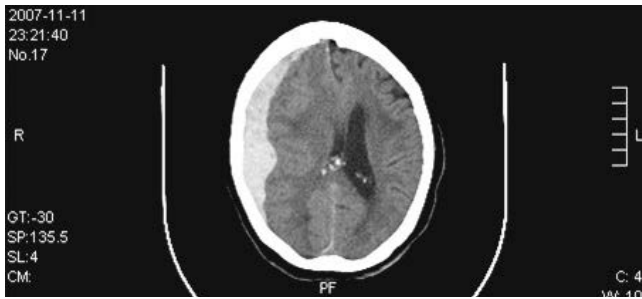
only in terms of targeted hemodynamic end points but also in terms of quantity and nature of fluid administration. Given that the extracellular space is four to five times larger than the plasma volume, large volume, isotonic crystalloid resuscitation is often required for trauma or burn patients to re-establish circulatory stability. Trauma, burns, or major surgery lead invariably to an obligatory loss of fluid into the intracellular or so-called third space compartment and an increase in the ratio of extracellular to plasma volume. Progressive brain swelling, increases in lung water, intra-abdominal hypertension, as well as immunologic and microcirculatory dysfunction can develop. The use of low-volume, hypertonic solutions may decrease the risk of these adverse events by restoring circulation and decreasing third space fluid sequestration, while preventing or minimizing the incidence of cerebral and pulmonary edema and abdominal compartment syndrome.

## Traumatic Brain Injury

Cerebral edema and intracranial hypertension often develop from traumatic brain injury (TBI) and are associated with poor outcome. Osmotherapy with mannitol remains the most widely recommended mode of treatment. However, experimental data indicate that hypertonic saline (HTS) (3%, 7.5%, 23.4%) can be as effective in reducing intracranial pressure and may have a longer duration of action. Prospective, randomized human trials assessing the use of HTS in patients with TBI, however, are limited. Vailet et al. evaluated 7.5% HTS versus mannitol in 20 patients with TBI and intracranial hypertension refractory to conventional therapy and found HTS to be more effective.<sup>1</sup> Cooper et al. compared a prehospital bolus of 250 mL of 7.5% HTS versus Lactated Ringer's solution in victims of traumatic brain injury.<sup>2</sup> Although there were no outcome differences between groups, patients in the HTS group had a prolonged period of sustained elevation in cerebral perfusion pressure, consistent with the aforementioned experimental studies. Although experimental and clinical data validate the effectiveness of HTS in reducing ICP, data proving improved outcomes are lacking.<sup>3</sup> A significant confounding variable is that the majority of patients studied also suffered from polytrauma, thus making it more difficult to differentiate the etiologies of morbidity and mortality.

## Acute Lung Injury/Adult Respiratory Syndrome/Immunomodulation

Acute lung injury and adult respiratory distress syndrome occur in as many as 40% of patients suffering from polytraumatic injuries. A cascade of inflammatory mediators released following the sequestration of activated polymorphonuclear neutrophils



**Figure 13.1** • A right-sided frontoparietal subdural hematoma with ventricular compression and evidence of increased intracranial pressure.

within the microcirculation of the lung is purported to be an important mechanism by which secondary injury occurs in the setting of trauma and hemorrhagic shock. Experimental studies have shown HTS-mediated immunomodulation, which suggests a role in mitigating the inflammatory process. Junger and colleagues found HTS (7.5% sodium chloride, 4 mL/kg) enhanced T-cell function in vitro and cell-mediated immune function in vivo in a murine model of hemorrhagic shock.<sup>4</sup> HTS also protected animals by improving survival from sepsis. Rizoli et al. noted a beneficial effect of HTS (4 mL/kg of 7.5% sodium chloride) in significantly reduced transpulmonary albumin leak, bronchioalveolar lavage fluid neutrophil counts, and the degree of histopathologic lung injury, when compared to Lactated Ringer's solution resuscitation in a rodent model of hemorrhagic shock.<sup>5</sup>

### Secondary Abdominal Compartment Syndrome

Abdominal compartment syndrome is defined as the presence of sustained intra-abdominal pressure elevation  $\geq 20$  mm Hg with or without abdominal perfusion pressure  $< 50$  mm Hg and associated with new-onset single or multiorgan system failure. Abdominal compartment syndrome can occur as a result of primary abdominal trauma or surgery or secondary to massive fluid resuscitation-induced visceral edema in non-trauma or burn patients, particularly in the setting of shock. The gut is prone to ischemia-reperfusion injury, and the subsequent increase in microvascular permeability leads to large quantities of free intraperitoneal fluid and subsequent intra-abdominal hypertension. Intra-abdominal hypertension and secondary abdominal compartment syndrome significantly

decrease cardiac output by diminishing preload and increasing systemic vascular resistance. Unintended intra-abdominal hypertension can also impair respiratory, renal, gastrointestinal, and hepatic function and lead to multiorgan system failure. Aggressive crystalloid fluid resuscitation in an attempt to counter these pathophysiologic changes often contributes to the development of abdominal compartment syndrome and has been termed “futile crystalloid preloading.” Some studies have suggested that more than 6 liters of crystalloid fluids within the first 24 hours of resuscitation of critically ill patients may result in a higher incidence of abdominal compartment syndrome and multiorgan system failure.<sup>6</sup> In this regard, it has been suggested that the use of HTS may be advantageous in minimizing intra-abdominal hypertension. Oda et al. compared the administration of hypertonic lactated saline versus standard Lactated Ringer's solution in patients who sustained burn injuries of greater than 40% of their body surface areas and found a significant decrease in the incidence of intra-abdominal hypertension and secondary abdominal compartment syndrome.<sup>7</sup> Improvements in oxygenation were also noted. Despite these preliminary findings, further randomized controlled studies are necessary before definitive recommendations can be made regarding the use of HTS to prevent secondary abdominal compartment syndrome.

### Types and Methods of Hypertonic Saline Administration

HTS tends to mobilize intracellular water, reduced cellular edema, and reduced overall volume requirements during resuscitation. Plasma volume is expanded, cardiac output is increased, and overall oxygen delivery is improved all relatively rapidly when compared with isotonic saline resuscitation. The most often used formulation of hypertonic solution is a combination of 7.5% sodium chloride (2400 mOsm/L saline) and 6% dextran 70, a colloid solution that exerts two to three times the colloid osmotic pressure of an equal concentration of human albumin. An infusion of 4 to 6 mL/kg over several hours appears to be safe and effective. Bolus doses of 250 mL of 7.5% sodium chloride over 10 to 15 minutes also appear to be well tolerated in clinical studies.<sup>8</sup> Table 13.1 details the characteristics of the most commonly administered HTS solutions.

### Complications of HTS Administration

HTS resuscitation can be associated with hyperosmolarity and hypernatremia. Serum osmolarity levels greater than 320 mOsm/L have been associated with acute renal failure during the use of mannitol; data are lacking regarding HTS

**TABLE 13.1** HTS Characteristics

HTS (%)	Na <sup>+</sup> /Cl <sup>-</sup> (mEq/L)	Osmolality (mOsm/L)	Maximum Infusion Rate
3	513	1030	100 mL/hr
5	855	1710	100 mL/hr
7.5	1282	2400	250 mL (bolus)
23.4	4000	8000	NA

HTS, hypertonic saline solution.

and these complications. Central pontine myelinolysis is a complication of the rapid correction of extracellular serum sodium levels in the setting of hypotonic hyponatremia. Retrospective studies, however, have failed to demonstrate central pontine myelinolysis either by magnetic resonance imaging or at postmortem examination. Other concerns with HTS administration include rebound intracranial hypertension and hyperchloremic metabolic acidosis.<sup>9</sup>

In conclusion, the use of HTS may offer a novel approach in caring for patients with traumatic brain injury, polytrauma, or burn injuries; however, its use must be tempered by the lack of clinically relevant outcome data. Current randomized, controlled trials may offer further insight into this type of therapy.<sup>10</sup>

### KEY MESSAGES

1. HTS can be of benefit in the management of traumatic brain injury by decreasing intracranial pressure.
2. Massive crystalloid resuscitation may result in a secondary abdominal compartment syndrome that can be mitigated by the use of HTS solutions.
3. Complications of HTS administration may include hyperchloremic metabolic acidosis, hyperosmolarity, and rebound intracranial hypertension.

### QUESTIONS

1. Hypertonic saline resuscitation for a patient with traumatic brain injury may result in which of the following complications?
  - A. Central pontine myelinolysis
  - B. Cerebral edema
  - C. Cerebral artery vasospasm
  - D. Rebound intracranial hypertension
  - E. Diabetes insipidus

Answer: D
2. A 33-year-old male receives hypertonic saline resuscitation following a 50% body surface area thermal injury. Which of the following physiologic parameters may be expected to decrease when compared to standard therapy with isotonic crystalloid solutions?
  - A. Intra-abdominal pressure
  - B. PaO<sub>2</sub>/fiO<sub>2</sub> ratio

- C. Urine output
- D. Cardiac output
- E. Gastric pH

Answer: A

3. Which of the following serum electrolyte abnormalities is more likely to occur when large volume fluid resuscitation is performed with Lactated Ringer's solution rather than with small volume hypertonic saline?
  - A. Hypomagnesemia
  - B. Hypocalcemia
  - C. Hypokalemia
  - D. Hyponatremia
  - E. Hypochloremia

Answer: D

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# Preoperative Liver Function Test Abnormalities

David M. Rothenberg

## CASE FORMAT: REFLECTION

A 39-year-old, 6-ft, 80-kg man presented for repair of his left anterior cruciate ligament following a skiing injury. The patient's past medical history was significant only for hypertension treated with hydrochlorothiazide. His past surgical history included a right inguinal hernia repair performed under inhalational general anesthesia 1 year prior to this admission. His social history included occasional alcohol use but no history of recreational drug use. The patient's vital signs were as follows: blood pressure, 140/90 mm Hg; heart rate, 88 beats per minute; respiratory rate, 12 breaths per minute; and his temperature was normal. The remainder of his physical examination was unremarkable.

The orthopaedic surgeon had ordered an array of laboratory tests including complete blood count, coagulation profile, serum electrolytes, and liver function tests (LFTs). The results of the laboratory tests were within normal limits with the exception of serum aspartate aminotransferase (AST), 65 IU/L (normal range, 10–34 IU/L) and alanine aminotransferase (ALT), 55 IU/L (normal range, 8–37 IU/L). Total bilirubin and alkaline phosphatase levels were within normal limits as was the internationalized normalized ratio (INR).

At the outpatient surgery center, the anesthesiologist was reluctant to perform an anesthetic because of the elevation in LFTs and recommended further workup of the patient's abnormal transaminase results.

## DISCUSSION

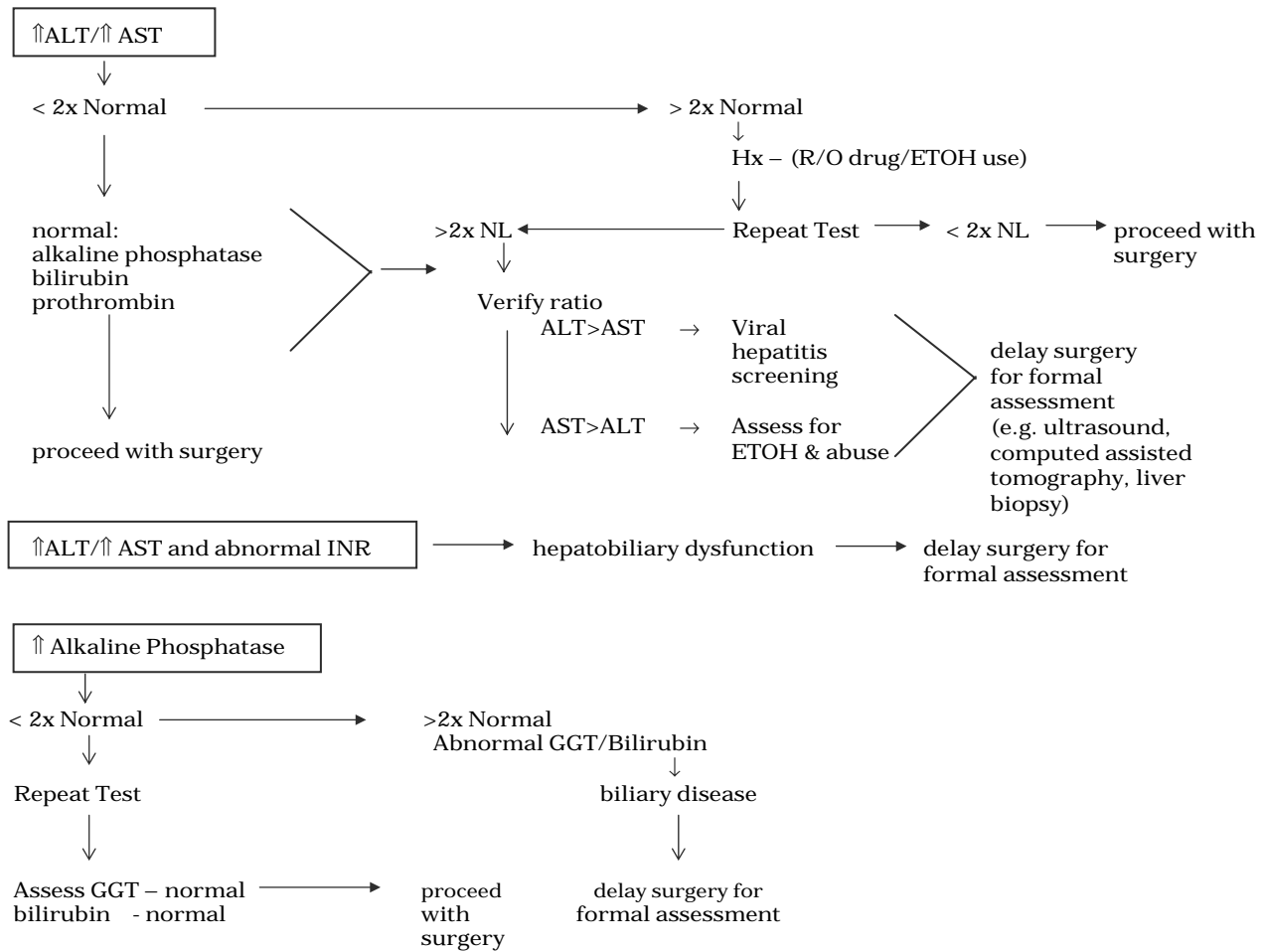
Patients with asymptomatic elevation in preoperative LFTs pose a dilemma for anesthesiologists in assessing perioperative hepatic risk, as prospective studies addressing this concern are lacking. The preoperative evaluation of risk for the development of postoperative hepatic dysfunction requires not only consideration of the magnitude of LFT abnormalities and whether or not active inflammatory or cholestatic disease exists, but also the nature of the surgical procedure planned.

The first question that must be asked regarding patients with asymptomatic elevation in LFTs is why the tests were initially ordered. Indiscriminate laboratory testing that reveals an increase in LFTs in an otherwise asymptomatic patient often leads to a delay in surgery based on the concern that administering an anesthetic may predispose the patient to postoperative hepatic dysfunction and subsequent morbidity or mortality. Abnormalities in LFTs including ALT, AST, and alkaline

phosphatase are present in a small proportion of the general population<sup>1</sup> and in as many as 36% of patients with psychiatric illnesses (in whom alcohol and illicit drug use may be a contributory factor).<sup>2</sup> The overall prevalence of clinically significant liver dysfunction in asymptomatic patients, however, is less than 1%.<sup>3</sup> Therefore, the decision to pursue further costly diagnostic workup is rarely indicated on the basis of laboratory results alone. Rather, the most logical approach to such a patient begins with a targeted history and physical examination eliciting signs and symptoms of active hepatobiliary disease. This includes findings such as right upper quadrant pain or tenderness and history of scleral icterus, pruritus, fatigue, anorexia, nausea, or vomiting. Stigmata of cirrhosis are often self-evident; however, the patient should also be queried regarding a history consistent with chronic hepatitis, Wilson's disease, hemochromatosis, diabetes, as well as a history of previous blood product transfusion. All medications, vitamins, and herbal remedies should be reviewed for potential hepatotoxic adverse effects, and the patient should be further questioned regarding the frequency and pattern of alcohol usage. Finally, a targeted history should also make reference to include illicit drug use, presence of tattoos, consumption of raw seafood, and sexual activity. If a detailed history and physical examination fail to suggest an etiology of the abnormal LFTs, it is reasonable to assume that the initial abnormalities were false positives and the tests should be repeated. Slight elevation in LFTs (less than twice normal values) do not warrant further testing before anesthesia or/and surgery. Greater elevation in LFTs requires a more detailed analysis of each specific abnormality. Abnormal LFTs in otherwise healthy patients can also reflect either a subclinical acute process, such as viral or toxin-mediated hepatitis or a chronic disorder such as chronic hepatitis.

Abnormalities of ALT and AST in combination tend to indicate hepatocellular injury.<sup>4,5</sup> An elevation in ALT greater than AST favors a diagnosis of viral hepatitis; an increase in AST greater than ALT tends to suggest alcohol-mediated hepatic injury. Increases in alkaline phosphatase and serum  $\gamma$ -glutamyltransferase indicate hepatobiliary disease, specifically extrahepatic bile duct obstruction or intrahepatic cholestasis. Further assessment of LFT abnormalities should include assessment of synthetic function. These tests entail measurement of serum bilirubin, albumin, and prothrombin time (as expressed by the INR); the latter being a sensitive index of hepatic synthetic function, often changing within 24 hours of hepatobiliary injury because of impaired synthesis of essential coagulation factors.

At this time, no prospective, randomized controlled trials have been performed to evaluate the perioperative risk of anesthesia or surgery in otherwise asymptomatic patients with



**Figure 14.1 • Asymptomatic Patient with Abnormal Liver Test Results for Surgery.** (From O'Connor CJ, Rothenberg D, Tumank KJ. Anesthesia and the hepatobiliary system. In Miller's Anesthesia, 6th Ed. New York: Elsevier, 2005.)

elevated LFTs. A suggested approach to such patients is delineated in Figure 14.1.

The preponderance of medical literature regarding perioperative morbidity and mortality in patients with acute hepatitis of any etiology suggests that elective surgery should be delayed until resolution of hepatic dysfunction. Patients with steatosis or steatohepatitis should also probably be considered to be at risk for developing postoperative liver failure, especially if they are to undergo major abdominal surgery. Additionally, patients with chronic hepatitis should be evaluated before elective surgery for any evidence of hepatic synthetic dysfunction. When surgery cannot be delayed or avoided, care must be taken during all phases of surgery to maintain hepatic vascular perfusion and to avoid factors that may precipitate liver failure, hepatic encephalopathy, or both.

Finally, patients with abnormal LFTs and a clinical constellation that is consistent with cirrhosis may be at particular risk for developing postoperative hepatic failure depending on the stage of cirrhosis as well as the type of surgery. Preoperative risk in patients with cirrhosis is often assessed by using the Child-Turcotte-Pugh scoring system (Table 14.1) and occasionally in conjunction with the model for end-stage liver disease scores (Table 14.2). Elective surgery should be considered contraindicated in patients with Child-Turcotte-Pugh classification C. Additionally, it is best to avoid elective

surgery in cirrhotic patients with an elevated INR, hypoalbuminemia, or preoperative infection or encephalopathy.

The actual surgical procedure itself, however, may be the most important risk factor for the development of postoperative hepatic dysfunction.<sup>6</sup> Abdominal surgery per se appears to significantly decrease total hepatic blood flow, particularly in patients with cirrhosis undergoing hepatic resection for hepatocellular carcinoma.<sup>7,8</sup> Cardiothoracic surgery is also associated with a high mortality rate in patients with pre-existing liver dysfunction.<sup>9</sup> Cardiopulmonary bypass may exacerbate pre-existing hepatic dysfunction by a multitude of mechanisms, including hepatic artery and portal venous hypoperfusion, low cardiac output syndrome, micro- or macroembolism, cytokine or oxygen free radical formation, and the influence of vasoactive and anesthetic drugs.

In assessing the patient described in this case, it is important to recognize that the peripheral nature of anterior cruciate ligament surgery imparts a minimal risk for this patient to develop postoperative liver failure, despite the slight elevation in this patient's LFTs. The magnitude of LFT elevation also indicates minimal risk of developing postoperative liver dysfunction and most likely represents either an effect of alcohol use or, less likely, that this is related to a cholestatic effect of hydrochlorothiazide. Repeating the LFTs is indicated primarily to rule out further increases indicative of ongoing or progressive pathology.

**TABLE 14.1** Modified Child-Turcotte-Pugh Scoring System

Parameters	Modified Child-Turcotte-Pugh Score*		
	1	2	3
Albumin (g/dL)	>3.5	1.8–3.5	<2.8
Prothrombin time Seconds prolonged	<4	4–6	>6
International normalized ratio	<1.7	1.7–2.3	>2.3
Bilirubin (mg/dL)†	<2	2–3	>3
Ascites	Absent	Slight–moderate	Tense
Encephalopathy	None	Grade I–II	Grade III–IV

\*Class A, = 5 to 6 points; B, = 7 to 9 points; and C, = 10 to 15 points.

†For cholestatic diseases (e.g., primarily biliary cirrhosis), the bilirubin level is disproportionate to the impairment in hepatic function, and an allowance should be made. For these conditions, assign 1 point for a bilirubin level less than 4 mg/dL, 2 points for a bilirubin level of 4 to 10 mg/dL, and 3 points for a bilirubin level greater than 10 mg/dL. Reproduced with permission from Pugh RNH, Murray-Lyon IM, Dawson JL, et al. Transection of oesophagus for bleeding of oesophageal varices. *Br J Surg* 1973;60:646–649.

## KEY MESSAGES

1. Asymptomatic elevation in LFTs may or may not pose a significant perioperative risk for the patient undergoing anesthesia.
2. Specific LFT abnormalities can indicate the influence of preoperative medications, alcohol use, or active inflammatory disease.
3. Preoperative LFTs should only be considered on patients who present with a history or physical evidence of hepatic dysfunction.
4. The decision to perform surgery and administer anesthesia to patients with abnormal LFTs should be predicated on the nature of the surgery and the magnitude of changes on the LFTs.

**TABLE 14.2** MELD Score Calculation

$$\text{MELD} = 3.78 [\text{Ln serum bilirubin (mg/dL)}] + 11.2 [\text{Ln INR}] + 9.57 [\text{Ln serum creatinine (mg/dL)}] + 6.43$$

In addition, the following are modifications of the MELD score:

- The maximum score given is 40. All values higher than 40 are given a score of 40.
- If the patient has been dialyzed twice within the last 7 days, the serum creatinine level used should be 4.
- Any value less than 1 is given a value of 1.

INR, internationalized normalized ratio; MELD, end-stage liver disease.

## QUESTIONS

1. Which of the following serum levels may be associated with increased perioperative morbidity?
  - A. ALT 55 IU/L
  - B. Bilirubin 3.6 mg%
  - C. INR 1.6
  - D. AST 90 IU/L
  - E. Alkaline phosphatase 42 mg%

Answer: D

2. A patient presenting for total hip replacement is noted to have clinical stigmata of cirrhosis including mild ascites. Preoperative laboratory values include a serum albumin level of 2.7 gm%, INR of 2.8, and a serum bilirubin level of 4 mg%. The most appropriate next step in this patient's care should be:
  - A. Therapeutic paracentesis
  - B. Preoperative plasma transfusion
  - C. Delay of surgery
  - D. Administration of 5% albumin
  - E. Avoidance of inhalational general anesthesia

Answer: C

3. Which of the following surgeries is associated with an increase in postoperative hepatic dysfunction in a patient with a preoperative history of chronic active hepatitis?
  - A. Pneumonectomy
  - B. Partial colectomy
  - C. Bilateral total knee replacement
  - D. Carotid endarterectomy
  - E. Total thyroidectomy

Answer: B

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# Perioperative Use of Albumin

W. Christopher Croley

## CASE FORMAT: REFLECTION

A 68-year-old, 60-kg male with a history of hypertension, hypercholesterolemia, and non-insulin-dependent diabetes presented for a left hemicolectomy. The patient was currently taking metoprolol, metformin, and simvastatin. He completed a bowel preparation consisting of clear liquids, a Fleet enema, and 4 liters of GoLYTELY on the day before his procedure. The patient reported a recent history of nausea, vomiting, fatigue, and a 5-kg weight loss. His preoperative assessment revealed the following normal vital signs: blood glucose, 108 mg/dL and hemoglobin, 13 gm/dL. Electrocardiogram readings showed normal sinus rhythm with possible left ventricular hypertrophy. On physical examination, the patient had clear lung fields, normal heart sounds, a Mallampati I airway, and was edentulous.

Preoperatively, the patient had two 16-gauge intravenous (IV) cannulae and a right radial arterial line inserted. Once inside the operating suite, standard monitors were applied and general anesthesia was induced with 180 mg of sodium thiopental, 250  $\mu$ g of fentanyl, and muscle relaxation was achieved with vecuronium 6 mg. The patient's trachea was easily intubated with a 7.5-mm endotracheal tube. Anesthesia was maintained with fentanyl (3  $\mu$ g/kg per hour), sevoflurane (inspired 1%–1.5%), and further increments of vecuronium were administered as required. After induction of anesthesia, a right internal jugular triple-lumen catheter was inserted under ultrasound guidance for central venous pressure (CVP) monitoring. His initial CVP was 2 mm Hg. His vital signs remained stable throughout the procedure with mean arterial blood pressures (MAPs) between 60 to 75 mm Hg and CVP values ranging from 1 to 15 mm Hg. Estimated blood loss for the 4-hour procedure was 900 mL. The patient received 4000 mL of Lactated Ringer's solution and 750 mL of 5% human albumin. His trachea was extubated at the end of the procedure, and he was transferred to the surgical intensive care unit for further monitoring. On arrival to the surgical intensive care unit, his vital signs were as follows: heart rate, 105 beats per minute; blood pressure, 85/40 mm Hg with a MAP of 55 mm Hg; respiratory rate, 24 breaths per minute; and CVP, 2 mm Hg. He received an additional 500 mL of 5% human albumin, which increased his CVP to 10 mm Hg and MAP to 70 mm Hg. The patient was monitored in the surgical intensive care unit for 1 day and was then transferred to the general surgical floor. He was discharged

home on the seventh postoperative day. On discharge from the hospital, his hemoglobin level was 9 gm/dL, and his creatinine and other laboratory measures were at their baseline values.

## CASE DISCUSSION

The debate on crystalloid versus colloid fluid resuscitation continues to elicit strong opinions from clinicians who are forced to deal with volume resuscitation of patients on a daily basis. Although human albumin has been used for more than 60 years, semi-synthetic colloid fluids have only been introduced relatively recently. Albumin and semi-synthetic solutions are available in various concentrations. Although human albumin has been used for many years, there are insufficient data from large clinical trials to demonstrate improvement in morbidity or mortality rates when using human albumin as a resuscitation fluid.

Human albumin preparations contain more than 95% albumin with a uniform molecular size (Table 15.1). The capillary membrane is fairly permeable to small ions (i.e.,  $\text{Na}^+$  and  $\text{Cl}^-$ ) but is relatively impermeable to larger molecules such as albumin. Therefore, it is postulated that colloids will remain in the intravascular space for a longer period of time than crystalloids. The duration that a colloid will affect plasma volume expansion is a function of the rate of colloid molecule loss from the circulation and by metabolism. Proponents of colloid fluid resuscitation argue that the increased duration of plasma volume expansion and decreased leaking of colloid molecules from the capillary membrane ultimately lead to less tissue edema, which may (in theory at least) benefit patient outcome. Human albumin has several disadvantages not associated with synthetic colloid products because it is a human-derived product (Table 15.2). Some of these disadvantages include expense, risk of transmission of infectious agents, and possible allergic reactions.

The Saline versus Albumin Fluid Evaluation trial is a randomized controlled trial of approximately 7000 patients that compared albumin and saline as resuscitation fluids and showed no difference in outcome between the two groups. This landmark trial is consistent with results of several other trials that have evaluated colloid versus crystalloid for fluid resuscitation and failed to demonstrate a significant mortality benefit.

Despite a lack of evidence demonstrating a clear benefit of colloid over crystalloid, some clinicians continue to use albumin

**TABLE 15.1** Composition of Commonly Used Crystalloid Fluids

Solution	Osmolarity (mOsm/L)	Na <sup>+</sup> (mmol/L)	Cl <sup>-</sup> (mmol/L)	K <sup>+</sup> (mmol/L)	Ca <sup>++</sup> (mmol/L)
0.9% Sodium chloride	308	154	154	-0-	-0-
Lactated Ringer's solution	309	147	156	4.0	2.2
Normasol	280	140	98	5	0

as a preferred resuscitation fluid. It is proposed that large volumes of crystalloid dilute plasma proteins, as well as plasma oncotic pressure, resulting in tissue and pulmonary edema. Clinically, the decrease in oncotic pressure and increase in tissue edema has not been proven to be detrimental in terms of patient mortality (Fig. 15.1).

For patients with limited IV access, albumin or other colloid fluids will expand plasma volume more rapidly than crystalloid and at a lower volume of total fluid infused. Outside of this particular indication, albumin should not be routinely used as a preferred resuscitation fluid because of lack of evidence of improved mortality, increased cost, and possible adverse events associated with administration. Future studies should aim to compare crystalloid versus colloid in terms of meaningful patient outcomes other than mortality. It will require careful systematic evaluation to identify specific clinical scenarios in which one or another type of fluid resuscitation will benefit the patient.

**KEY MESSAGES**

1. No mortality differences have been shown between patients who receive crystalloid versus colloid fluid for resuscitation in the perioperative period.
2. Human albumin is one of several colloid fluids available for volume resuscitation.
3. Limitations of albumin administration include acquisition cost, possible allergic reactions, and infectious risks.

**QUESTIONS**

1. You are preparing to transport a 69-year-old female to the endoscopy suite from the intensive care unit for an upper endoscopy when she begins to vomit bright red blood, becomes tachycardic to 140 beats per minute,

**TABLE 15.2** Concerns with Human Albumin Administration

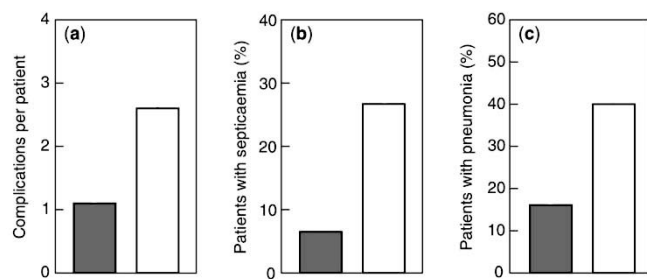
- Relatively expensive
- Possible transmission of infectious agents
- Allergic reactions
- Limited supply

and has a weak radial pulse. The patient has one 22-gauge IV in her left forearm, and four units of blood are on hold in the blood bank. The most appropriate initial fluid given the following options would be:

- A. 250 mL of 0.9 normal saline
- B. 500 mL of dextran
- C. 250 mL of 5% human albumin
- D. 100 mL of 3% hypertonic saline

Answer: C. This patient has one small-bore IV line and will need rapid volume expansion while blood is ordered from the blood bank and additional IV access is established; 5% albumin will provide greater plasma volume expansion in a shorter period of time than crystalloid. Dextran may have deleterious effects on platelets and worsen bleeding. Hypertonic saline is not indicated for rapid volume expansion during hypovolemic shock.

2. All of the following affect duration of albumin for plasma volume expansion except:
  - A. Continued resuscitation with 0.9% normal saline
  - B. Hypoalbuminemia
  - C. Rate of loss from circulation
  - D. Metabolism of administered albumin
  - E. None of the above



**Figure 15.1** • (A) Mean complications per patient and percentage of patients, *p* value <0.008. Graph (B) depicts the percentage of patients with septicemia, *p* value <0.04. Graph (C) depicts patients with pneumonia, *p* value <0.05. These were each randomized controlled trials comparing albumin versus no albumin in patients with hypoalbuminemia that required total parenteral nutrition. Gray, albumin; white, no albumin. (Adapted from Haynes GR, Navickis RJ, Wilkes MM. Albumin administration—what is the evidence of clinical benefit? A systematic review of randomized controlled trial. *Eur J Anest* 2003;20:771–793.)

Answer: B. Continued resuscitation with 0.9% normal saline will dilute the plasma oncotic pressure and decrease the amount of time that the albumin has an effect on plasma volume expansion; hypoalbuminemia has no correlation with how long the albumin is administered, as resuscitation fluid will remain intravascular.

3. Problems associated with albumin include all of the following except:

- A. Increased cost
- B. Limited availability of product
- C. Potential allergic reactions
- D. Potential transmission of infectious organisms
- E. Difficulty cross-matching blood after its administration

Answer: E. All answers listed are problems associated with albumin administration.

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# Neurologic Complications of Peripheral Nerve Blockade

Christopher J. O'Connor

## CASE FORMAT: REFLECTION

A 55-year-old, 90-kg man with a history of hypertension, non-insulin-dependent diabetes mellitus, and shoulder pain presented for right total shoulder arthroplasty. He had previously undergone inguinal hernia repair and an appendectomy without anesthetic complications. His regular medications included metoprolol, valsartan, metformin, and naproxen. The preoperative evaluation identified left ventricular hypertrophy on his electrocardiogram, his nonfasting serum glucose level was 170 mg/dL, and hemoglobin concentration was 12.9 mg/dL. Initially, the patient's vital signs were as follows: blood pressure, 136/80 mm Hg; heart rate, 65 beats per minute; arterial oxygen saturation, 98%; and respiratory rate, 18 breaths per minute. Neurologic function of the operative arm was normal.

The anesthetic plan comprised an interscalene block (to be inserted preoperatively) and a continuous interscalene catheter for postoperative analgesia, in conjunction with general anesthesia and tracheal intubation.

An intravenous catheter was placed in the contralateral arm, and standard monitors were applied. Oxygen was administered at 3 L per minute by nasal cannulae, and incremental doses of midazolam (0.5 mg) and fentanyl (25 mcg) were administered according to the anesthesiologist's clinical judgment. A nerve stimulator was prepared by attaching the grounding lead to a surface electrode, the patient's chest, and a 17-gauge insulated Tuohy needle was primed with local anesthetic. The right side of the patient's neck was prepared using sterile precautions. Local anesthetic (LA) (lidocaine 2%, 2 mL) was injected subcutaneously at the interscalene groove, and the Tuohy needle was advanced until the characteristic musculocutaneous nerve response (biceps muscle contraction) was achieved. Following negative aspiration of the needle for blood, 35 mL of 0.5% ropivacaine with epinephrine (1/10,000) was incrementally injected with serial aspirations after each 3-mL injection. No change in heart rate or sensorium was noted. Following completion of the LA injection and as the interscalene catheter was inserted through the Tuohy needle, the patient's left hand and arm began to twitch, and he became unresponsive to verbal command. The needle was immediately withdrawn, and midazolam (3 mg) was administered, while oxygen (100%) was given using positive-pressure bag/mask ventilation. The twitch-

ing resolved immediately, and within 15 minutes, the patient was once more responsive and oriented. Sensory and motor testing of the right arm and shoulder revealed dense anesthesia.

The patient underwent uncomplicated total shoulder arthroplasty and recovery. Five days later, however, he reported a sensory paresthesiae in the median nerve distribution of his right arm. Nerve conduction studies demonstrated mild conduction disturbance of his right median nerve that resolved completely over 3 weeks. His recovery was otherwise uneventful.

## DISCUSSION

### Central Nervous System Toxicity

Central nervous system (CNS) toxicity follows vascular absorption or intravascular injection of LA and manifests as a change in the patient's sensorium or mental status, the patient's perception of a metallic taste, tinnitus, or as an overt grand mal seizure. CNS toxicity tends to precede cardiovascular toxicity and is typically short lived. Appropriate management entails administration of small doses of midazolam or sodium thiopental and support of ventilation and oxygenation during the (usually) brief duration of the seizure or altered mental status. If the patient's mental status returns to baseline promptly, and if no injuries are sustained during the event, it is reasonable to proceed with surgery.

### Peripheral Nerve Injury

Nerve injury following peripheral nerve blockade (PNB) is gratifyingly uncommon. Published investigations of the incidence of this complication are limited by study design and inconsistent neurodiagnostic follow-up. Moreover, it is often difficult to determine the precise etiology of postoperative neurologic deficits (PNB-related vs. surgical). Despite these limitations, certain conclusions can be drawn. The mechanism of nerve injury after surgery accompanied by PNB can be related to several factors, including block-related events (e.g., needle trauma, intraneural injection [INI],<sup>1,2</sup> and LA neurotoxicity), surgical factors (e.g., surgical trauma, stretch injuries, and the impact of tourniquets, hematoma, compressive dressings, and positioning), and the impact of pre-existing conditions (e.g., bony deformities and peripheral neuropathy).



Needle trauma is probably uncommon, whereas INI appears to be the likely mechanism of block-related nerve injury in most patients. High injection pressures<sup>2</sup> and severe pain on injection indicate INI and subsequent fascicle disruption. The peripheral nerve is a complex structure bounded by the epineurium that encases multiple nerve fascicles surrounded by a perineural layer. Each fascicle contains myelinated neurons that can be damaged by intrafascicular injection of LA. This appears to produce neurologic injury by inducing swelling and edema of the fascicle with subsequent neurovascular compromise and possibly by direct LA toxicity.<sup>3,4</sup> Interestingly, Bigeleisen demonstrated that 81% of patients undergoing ultrasound (US)-guided axillary block had evidence of INI in at least one nerve, with no subsequent evidence of neurologic injury,<sup>3</sup> suggesting that small-volume INI does not produce clinical nerve injury and occurs commonly without a clinically detectable adverse outcome. This finding is borne out by clinicians experienced with US-guided PNB. Although US may facilitate accurate LA deposition around rather than within the nerve, there are no clinical data to validate that assumption. Bigeleisen's findings also imply that injection beneath the perineurium is the probable site of injury from INI.

In addition to block-related injury, surgical factors appear to be especially important in producing neurologic deficits. Experimental data, as well as electrophysiologic studies in patients have shown the compressive and neuronal ischemic effects of excessive tourniquet duration and inflation pressure on peripheral nerves. Horlocker et al.<sup>5</sup> and Fanelli et al.<sup>6</sup> demonstrated that duration of tourniquet inflation and pressures >400 mm Hg, respectively, were associated with an increased incidence of postoperative neurologic deficit after limb surgery. Retractor injury to the femoral nerve during hip arthroplasty, stretch injury of the brachial plexus during shoulder arthroplasty, and peroneal nerve injury related to preoperative valgus deformities and flexion contractures after

knee arthroplasty, are additional mechanisms that can result in postoperative neurologic deficit unrelated to PNB. In fact, Horlocker et al.<sup>7</sup> noted that 89% of neurologic deficits after 1614 axillary blocks were related to the surgical procedure itself, a finding consistent with other clinical reports. In addition, 4% of patients undergoing shoulder arthroplasty sustain brachial plexus injuries in the absence of PNB, again suggesting surgical nerve injury.<sup>8</sup> Candido et al. observed that of the 4.4% of 684 patients experiencing paresthesia after interscalene block for shoulder surgery, 45% were located at the site of the block, and 23% were in the distribution of the greater auricular nerve; more serious distal sensorimotor neuropathies were thus infrequent.<sup>9</sup> Finally, although preoperative neuropathy and nerve localization techniques can be associated with postoperative nerve injury, well-designed prospective studies have failed to show any consistent relationship between diabetes, pre-existing neuropathy, or the use of nerve localization techniques and the incidence of neurologic deficit after PNB.

Most postoperative neurologic complaints manifest within the first 48 hours after surgery. They are typically sensory deficits and usually resolve within 2 to 4 weeks, although rarely, deficits can require up to 9 months for complete recovery. Nerve conduction studies (NCS) and electromyography (EMG) typically reveal conduction delays consistent with neuropraxia, a temporary injury pattern associated with functional recovery. Assessment of neurologic deficits should include a careful neurologic examination, and, in most cases, NCS and EMG. Repeat studies are commonly performed at 4 to 6 weeks, after which clinical assessment appears to suffice in the absence of severe motor deficits.

Determining the incidence of block-related nerve injury is difficult (Tables 16.1 to 16.3). However, prospective analyses of more than 70,000 patients have indicated an incidence of 0.02%. This is likely to be an underestimate caused by self-reporting. Other prospective and retrospective analyses have

**TABLE 16.1** Incidence of Neurologic Injury After Peripheral Nerve Blockade: Single-Injection Nerve Block

Author	Patient No.	Study Design	Incidence (F/U Time)	Block Type		Recovery (at mos)
				UE	LE	
Auroy, 2002	50,223	Pro	0.02% (NS)	All	All	42% (6 mo)
Auroy, 1997	21,278	Pro	0.02% (48 h)	All	All	100%
Fanelli, 1999	3996	Pro	1.7% (1 mo)	ISB, Ax	F-SB	99% (3 mo)
Stan, 1995	1995	Pro	0.2% (? 1 wk)	Ax	—	100% (2 mo)
Klein, 2002	2382	Pro	0.25% (7 d)	All, ISB	F-SB	100% (3 mo)
Horlocker, 1999	1614	Retro	8.4% (2 wk)	Ax	—	100% (5 mo)
Candido, 2006	693	Pro	8.5% (2 d–1 mo)	ISB	—	97% (4 mo)
Bishop, 2005	568	Retro	2.3% (2 wk)	ISB		91% (6 mo)
Giaufre, 1996	1995	Pro	0%	All	All	—

Ax, axillary; F-SB, femoral-sciatic block; F/U, follow-up; ISB, interscalene block; LE, lower extremity; NS, not significant; pro, prospective; retro, retrospective; UE, upper extremity.

**TABLE 16.2** Incidence of Neurologic Injury After Peripheral Nerve Blockade: Continuous Catheters

Author	Patient No.	Study Design	Incidence (%)	Block Type		Recovery (at mos)	Comments
				UE	LE		
Capdevila, 2005	1416	Pro	0.2% (24 h)	All	All	100% (3 mo)	
Borgeat, 2003	700	Pro	8% (10 d)	ISC	—	100% (7 mo)	
Borgeat, 2001	530 (SS+CC)	Pro	14% (10 d)	ISC	—	99% (9 mo)	No difference SS and CC
Swenson, 2006	620	Pro	0.3% (1 wk)	ISC	FIC, SC	100% (2 mo)	
Bergman, 2003	405	Retro	1% (postop)	AxC	—	100%	
Sada, 1983	597	Pro	0.5% (?)	AxC	—	?	
Grant, 2001	228	Pro	0% (1, 7 d)	ISC	?	—	
Singelyn, 1999	446	Pro	0.1% (?)	—	FC	?	
Cuvillon, 2001	211	Pro	0.4% (6 wk)	—	FC	99% (12 mo)	

FC, femoral catheter; FIC, fascia iliaca catheter; F/U, follow-up; ISB, interscalene block; ISC, interscalene catheter; LE, lower extremity; NS, not significant; sc, sciatic catheter; UE, upper extremity.

shown greater complication rates of 0% to 8% after single-injection upper extremity blockade and rates <0.5% for lower extremity blocks. Studies of continuous catheter (CC) techniques have similarly revealed low neurologic injury rates. Capdevilla et al.<sup>10</sup> demonstrated a 0.21% incidence of nerve injuries after 1416 upper and lower extremity CC techniques as did Swenson et al.<sup>11</sup> in a similar analysis of 620 CC techniques.

In conclusion, nerve injury can occur after PNB but is infrequent, is typically a transient sensory neuropraxia, and may be related to surgical (rather than block-related) mechanisms.

It may result from INI, a complication that can be minimized by discontinuing injection when either high injection pressures or pain are encountered, and it appears unrelated to the type of nerve localization technique employed. Whether US guidance will decrease the already low incidence of these complications has yet to be determined. It certainly holds promise for visual, real-time assessment of needle placement and LA deposition. Ultimately, as long as needles, nerves, and local anesthetics are in close proximity, the potential for nerve injury will exist.

**TABLE 16.3** Pattern and Causality of Nerve Lesions: Single Injection

Author	Injury Pattern/Nerve Involvement	Block Type		Anesthesia vs Surgery Cause
		UE	LE	
Auroy, 2002	Per neuropathy	All	All	Not specified
Auroy, 1997	Not specified	All	All	Not specified
Fanelli, 1999	Not specified	ISB, Ax	F-SB	Not specified
Stan, 1995	1 ulnar/MC paresthesia	Ax	—	0.2% because of block
Klein, 2002	ISB-RN injury SCB-UN Injury	All, ISB	F-SB	50% clearly surgical
Horlocker, 1999	Pain/numbness: UN (4), RN, MN	Ax	—	88% because of surgery
Candido, 2006	Paresthesia: ISB Site, aur ner, thumb	ISB	—	54% because of block
Bishop, 2005	Sensory neuropathy ulnar 5/10	ISB	—	Not specified
Schroeder, 1996	Not specified	All	—	72% because of surgery

aur ner, auricular nerve; Ax, axillary; blk, block; F-SB, femoral-sciatic block; ISB, interscalene block; LE, lower extremity; MC, musculocutaneous; MN, median nerve; Per, peripheral; RN, radial nerve; UE, upper extremity; UN, ulnar nerve.

## KEY MESSAGES

1. Seizures are unpredictable but not uncommon complications of PNB. They are typically brief in duration, have few sequelae, and are easily managed with conservative therapy, including sedative/hypnotics in small doses, supplemental oxygen, and airway support.
2. Serious nerve injury after PNBs is rare and is typically sensory in nature. Such injury may be related to the nerve block itself (i.e., primarily intraneural injection, rarely needle trauma), direct surgical injury, or tourniquet-related nerve ischemia. It usually resolves in 3 to 6 weeks, although rarely sensorimotor lesions can last as long as 9 months.
3. Evaluation of persistent nerve injury after extremity surgery using PNB entails careful clinical assessment within 48 hours of surgery, NCS, EMG, and clinical evaluation at 2 and 6 weeks postoperatively. NCS and EMG help to estimate the severity and location of the lesion and the time course and likelihood of recovery but may not reveal its etiology (e.g., surgery vs. block-related nerve injury).

## QUESTIONS

1. The most appropriate evaluation of persistent paresthesia after surgery involving PNB includes:
  - A. MRI of the involved extremity
  - B. Careful observation for 4 weeks
  - C. Somatosensory-evoked potential measurements
  - D. EMG and NCS
  - E. Surgical re-exploration of the involved limb

Answer: D.
2. Most postoperative neurologic complaints after PNB and orthopaedic surgery:
  - A. Manifest 96 hours after surgery
  - B. Resolve within 1 week
  - C. Are usually motor deficits
  - D. Represent neuropraxia of the involved nerves
  - E. Are secondary to the nerve block

Answer: D

3. The mechanism of peripheral nerve injury after PNB and orthopaedic surgery most likely results from:
  - A. The use of paresthesia-seeking techniques
  - B. Needle trauma
  - C. The compressive effects of dressings
  - D. Local anesthetic toxicity
  - E. Surgical factors

Answer: E

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# Peripheral Nerve Block Versus Epidural Analgesia for Total Knee Arthroplasty

Asokumar Buvanendran

## CASE FORMAT: REFLECTION

A 62-year-old, 5'10" male weighing 122 kg presented to the anesthesia preoperative clinic 2 weeks before scheduled right total knee arthroplasty (TKA) for osteoarthritis. He expressed major concerns regarding postoperative pain control and recollected severe postoperative pain from his previous left TKA with poor range of motion currently in addition to chronic pain of his left knee. The patient's past medical history was significant only for hypertension and sleep apnea. His medications included metoprolol and non-steroidal anti-inflammatory drugs (NSAIDs); the latter had been discontinued 1 week before his visit to the preanesthesia clinic because of concerns regarding perioperative bleeding. He had a continuous positive airway pressure (CPAP) machine, which he used most nights. The remaining history, physical examination, and diagnostic workup did not indicate cardiac disease. Physical examination revealed an obese, cooperative patient with a Mallampati class III airway and normal vital signs.

The patient was very concerned about stopping the NSAID, as it was the only drug providing him with pain relief for his right knee arthritis. He was willing to discuss any option that would provide him with adequate pain relief and also a better functional outcome than that following his previous TKR.

## CASE DISCUSSION

TKA is a very effective treatment modality for severe chronic osteoarthritis of the knee. This procedure has become increasingly common over the past 2 decades.<sup>1</sup> In 2002 alone, more than 350,000 primary unilateral TKAs were performed.<sup>1</sup> This number has escalated to about 441,000 in 2004 and is expected to increase to 3.5 million by 2030.<sup>1</sup> This dramatic rise in the utilization rate for TKA can be attributed to an increasing elderly population and increased usage because of advances in surgical, anesthetic, and analgesic techniques. These advances have collectively contributed to decreased blood loss, less postoperative pain, a shorter duration of hospital stay, and improved functional outcome. The duration of hospital stay after TKA has decreased from an average of 7 to 10 days in the early 1990s to an average of 2 to 4 days currently.<sup>2</sup> The remainder of this discussion addresses the anesthetic management of this challenging patient.

## Neuraxial Anesthesia and Analgesia

Although general anesthesia is still practiced in many hospitals for joint replacement, this trend is gradually decreasing as clinical studies have shown a greater incidence of adverse effects associated with general anesthesia and intravenous opioids compared with regional anesthesia/analgesia.<sup>3</sup> TKA is associated with severe postoperative pain, which interferes with early mobility and physical therapy, thereby affecting both short- and long-term patient outcomes. With the widespread use of regional anesthetic techniques, combined spinal epidural anesthesia followed by continuous and patient-controlled epidural analgesia has become a common anesthetic/analgesic procedure for joint replacement surgeries. Epidural analgesia has been shown to reduce postoperative blood loss, provide superior pain control, and improve postoperative functional outcome in comparison with intravenous patient-controlled analgesia.<sup>4</sup> Epidural analgesic solutions that are commonly used include opioids such as fentanyl, local anesthetics such as bupivacaine (many hospitals currently use ropivacaine because of its preferential sensory blockade properties and cardiovascular safety), or a combination of the two. Common adverse effects associated with epidural analgesia include hypotension, urinary retention, pruritus, nausea, vomiting, and headache. Significant intraoperative hypotension can lead to postoperative nausea and vomiting and can also be associated with decreased postoperative cognitive function. This may be detrimental to initiation of early physical therapy, which is crucial for improved knee range of motion. Serious adverse effects such as epidural hematoma and the associated nerve damage, respiratory depression, and infection have also been reported.

If the patient in the case presented consents to neuraxial anesthesia, a reasonable approach would be to perform combined spinal epidural using bupivacaine (10–15 mg) and fentanyl 25 µg for the spinal anesthetic because of their synergistic analgesia. Given this patient's history of sleep apnea, caution is advisable as administration of opioids intrathecally can trigger respiratory depression. Administration of a short-acting opioid intrathecally can be safe but requires appropriate monitoring postoperatively. In addition, this patient should receive an appropriate multimodal regimen (Table 17.1). Postoperative analgesia can be maintained with a local anesthetic alone or in combination with clonidine (α<sub>2</sub>-agonist at low doses) as an adjuvant, thereby avoiding narcotics as the additive in the epidural mixture because of his history of sleep apnea. The patient should be monitored while using CPAP for respiratory parameters. As the patient undergoes rehabilitation, the epidural solution can be titrated to provide analgesia.

**TABLE 17.1** Recommended Multimodal Drugs

Drug	Preoperative and Intraoperative	Postoperative
Acetaminophen	1000 mg	500–1000 mg three times daily
COX-2 inhibitor: celecoxib	400 mg 2 hours before surgery	200 mg twice per day
Ketamine	20–70 mg IV	
Gabapentin or pregabalin	600 mg or 100 mg respectively	300 or 75 twice per day
Clonidine	100 µg PNB	
Clonidine	10 µg via epidural	

IV, intravenous; PNB, peripheral nerve blockade.

The epidural catheter can be removed on the third postoperative day or earlier depending on his achievement of discharge criteria set by the physiotherapist. The subject of deep vein thrombosis (DVT) prophylaxis for joint arthroplasty is controversial with some authorities advocating aspirin alone, especially for patients undergoing minimally invasive joint replacement.

The risk of developing a hematoma in the epidural space is greater in patients who receive low-molecular-weight heparin (LMWH) postoperatively for DVT prophylaxis, especially after surgery involving the lower limbs.<sup>9,10</sup> The dramatic increase in the use of LMWH in the early 2000s for DVT prophylaxis influenced the movement toward peripheral nerve blockade (PNB) (and use of continuous catheter techniques) for pain after orthopaedic procedures. Thus, the use of LMWH and other anticoagulants has been an important determinant of how postoperative analgesia is provided after total joint replacement.

## PNB

PNB of the major nerves supplying the lower extremities has emerged as a good alternative technique to an epidural for providing postoperative analgesia following procedures on the lower limb, especially in view of the current anticoagulation guidelines. PNB can be achieved by “single-shot” blockade or by continuous infusion. For lower limb surgeries, a femoral nerve block, a sciatic nerve block, an obturator nerve block, or a “three-in-one” block can be performed. Femoral nerve blocks are most commonly used for knee arthroplasties, either alone or in combination with a sciatic nerve block. After completion of the femoral nerve block, the patient is turned laterally for placement of a sciatic perineural catheter using a gluteal approach. Anatomically, an obturator nerve block in combination with a femoral nerve block provides superior analgesia compared with femoral plus sciatic nerve block. Performing an effective obturator nerve block is challenging. A “three-in-one” block is intended to block the lateral femoral cutaneous, the femoral, and the obturator nerves using a single injection.

Several studies have compared the analgesic efficacy and incidence of adverse effects of PNBs (femoral alone or femoral plus sciatic) versus epidural analgesia. In a systematic review of studies that compared the two techniques, Fowler et al. con-

cluded that the analgesic efficacy of epidural and PNB techniques was similar but that the incidence of adverse effects (hypotension, urinary retention, and nerve injury) was less for PNB.<sup>5</sup> Nerve injuries associated with PNB present much less patient morbidity than a neuraxial injury. The review also evaluated the potential benefit of combining a sciatic block with a femoral block and concluded that there was no additional benefit.<sup>5</sup> Although the lumbar plexus block has greater consistency with regard to blocking the obturator nerve compared to the infrainguinal femoral block (three-in-one), it is unclear as to whether there is any benefit in adding the obturator block.<sup>6</sup> The incidence of quadriceps weakness with PNBs is greater and can therefore interfere with early mobilization of the patient, but there appears to be no difference in rehabilitative outcomes for the two groups at the time of discharge.<sup>6</sup> Only limited evidence exists on whether continuous femoral nerve block is more effective than a single-shot femoral block. In one randomized trial by Salinas et al., continuous femoral block (vs. single shot) lessened pain scores and increased opioid consumption significantly; however, the duration of hospital stay and functional outcome did not differ between the two groups.<sup>7</sup> Although the mechanism is not clear,<sup>8</sup> the addition of clonidine 100 µg to PNB leads to prolongation of analgesic effect.

In the case presented herein, a reasonable alternative approach would be to insert femoral nerve and sciatic nerve catheters preoperatively. This combination could be used to provide adequate anesthesia for TKA either alone or with a mini-dose single-dose of spinal anesthetic. The local anesthetic concentration in the two peripheral catheters should be low so that patients can participate actively in their physiotherapy. It is also important to administer neuronal blockade as one element of a multimodal regimen that is adjusted in response to patient recovery throughout the perioperative period.

## Opioids and Obstructive Sleep Apnea

A known or presumptive diagnosis of obstructive sleep apnea (OSA) in a patient scheduled for surgery can influence the choice of anesthetic as well as postoperative analgesic management. In every obese adult patient, preoperative assessment should include questions on nocturnal snoring, and/or

**TABLE 17.2** Screening Questions for Sleep Apnea

- Do you snore excessively?
- Is your sleep refreshing?
- Do you have periods when you stop breathing while sleeping?

snorting and/or apnea, and daytime sleepiness (Table 17.2). Patients with OSA are particularly sensitive to the depressant effects of opioids, sedatives, and tranquilizers.<sup>11,12</sup> Opioids have been shown to increase the effects of sleep and decrease arousal mechanisms. In a patient without OSA, the ensuing hypoxemia and hypercarbia after the use of opioids and other sedatives trigger carotid and brainstem chemoreceptors to increase respiratory drive. In individuals with OSA, however, this physiologic response is vulnerable to the effects of opioids and other sedatives. In these patients, it is recommended that opioid analgesia should be avoided, and a multimodal analgesic regimen, which includes regional analgesia, should be used during the postoperative period.<sup>13</sup> It is important that such patients (as in the case described) continue their CPAP settings during the perioperative period, and oxygen saturation should be monitored continuously. Given the severity of postoperative pain associated with TKA, judicious administration of opioids may be necessary even in the presence of a functioning PNB.

### Multimodal Analgesia for TKA

Tissue inflammation resulting from surgery triggers the production of prostaglandins (PG). Prostaglandins, particularly PGE<sub>2</sub>, mediate pain by sensitizing the peripheral nociceptors to mechanical and chemical mediators of pain. Prostaglandins have also been shown to play a role in central sensitization. One isoenzyme of cyclooxygenase (COX-2) is primarily responsible for the production of PGE<sub>2</sub>. Selective COX-2 inhibitors decrease postoperative inflammation and pain and improve the overall functional outcome in patients after TKA.<sup>14,15</sup> Unlike other NSAIDs, selective COX-2 inhibitors such as celecoxib, do not compromise hemostasis; therefore, patients can continue to take celecoxib until the day of surgery and continue this regimen into the postoperative period. This presents one solution to the concerns expressed by the patient in this case. Discontinuing NSAIDs before surgery can lead to increased preoperative pain (osteoarthritis flare-up), and in turn, to increased postoperative pain scores. Patients who discontinue NSAIDs should be started on COX-2 inhibitors before surgery and for 10 to 14 days (for suggested doses, see Table 17.1) postoperatively until the inflammatory response to surgery has resolved. Pregabalin is an  $\alpha_2\text{-}\delta$  ligand that can act in synergy with COX-2 inhibitors to decrease postoperative hyperalgesia. Randomized controlled trials conducted in the perioperative setting in orthopaedic populations, both with gabapentin and pregabalin, have demonstrated an opioid-sparing effect (10%–20%). However, neither of these drugs alone or in combination can completely replace opioids for pri-

mary analgesia. Nevertheless, they are valuable elements of a multimodal approach to postoperative pain management. In addition, the use of pregabalin or gabapentin may decrease the incidence of chronic pain developing after knee surgery<sup>1</sup> (as in the case described). Patients who already have chronic pain from a previous surgery and are undergoing another surgical procedure are at a greater risk of developing an adverse outcome. Therefore, the perioperative physician should make every attempt to attenuate the surgical response, both humeral and neuronal, so that the patient can have an improved outcome. Other agents that could be used in the perioperative period for this patient include a round-the-clock regimen of acetaminophen (not exceeding 4 g/day), magnesium (N-methyl-D-aspartate antagonist), and vitamin C (antioxidant).

### SUMMARY

Patients undergoing TKA should be offered a COX-2 inhibitor until the day of surgery to relieve pain from osteoarthritis. A multimodal analgesic regimen should be applied and adjusted during the perioperative period.<sup>16</sup> Postoperative management should include either a femoral nerve catheter or an epidural to optimize analgesia, so that patients can undergo aggressive physical therapy for an improved functional outcome.

### KEY MESSAGES

1. Postoperative analgesia for patients undergoing TKA is vital for improved long-term outcome. Either PNB or an epidural can safely be instituted.
2. Patients with OSA present a significant challenge to anesthesiologists, and caution needs to be exercised in administering opioids and sedatives.
3. Acute postoperative pain is associated with an increased likelihood of developing chronic pain. It is likely that an effective multimodal analgesic regimen including neuraxial or PNB decreases the incidence of persistent postsurgical pain.

### QUESTIONS

1. Which of the following statements is true?
  - A. Poor postoperative pain control surgery will lead to good outcome.
  - B. Opioids can be safely administered in patients with sleep apnea.
  - C. Excellent postoperative pain control has been associated with improved functional outcomes.
  - D. PNBs should not be performed in orthopaedic patients.

Answer: C

## 2. Pregabalin acts at which receptor?

- A. N-methyl-D-aspartate receptor
- B. Aminobutyric acid receptor
- C.  $\alpha_2$ - $\delta$  subunit of calcium channel
- D. Inhibits prostaglandins
- E. Acts at the  $\alpha_2$  channel

Answer: C

## 3. Obese patients need to be asked the following questions except:

- A. History of snoring
- B. History of waking up in the night
- C. History of lethargy early in the morning and falling sleep during the day
- D. Do not bring the CPAP machine they use at home to the hospital

Answer: D

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# Paravertebral Nerve Blockade for Thoracic Surgery

Adrienne Wells

## CASE FORMAT: REFLECTION

A 72-year-old, 65-kg female with a history of dyspnea, productive cough, and fatigue presented for a left lower lobectomy for lung cancer. Her medical history was significant for a 90 pack-year smoking history, coronary artery stent placement following an acute myocardial infarction 3 months previously, and obstructive lung disease. Her medications included metoprolol, salmeterol/fluticasone inhaler, lovastatin, aspirin, and clopidogrel.

Preoperative evaluation revealed a frail elderly woman who was sitting up in bed, receiving oxygen by nasal cannulae. She was slightly dyspneic but able to complete sentences and carry on a conversation. Her airway examination was normal, but lung auscultation revealed coarse breath sounds throughout and decreased breath sounds at the left base. The patient's heart sounds were normal, and the results of her laboratory tests were within normal limits, except for hemoglobin concentration (16 gm/dL) and carbon dioxide content of 34 mEq/dL. Her echocardiogram showed evidence of an old inferior myocardial infarction. Her pulmonary function tests demonstrated significant obstructive disease, and SpO<sub>2</sub> on 4 liters of oxygen via nasal cannula was 97%. The decision was made to include a regional technique as part of her plan for postoperative analgesia. Because she may have had impaired hemostatic function caused by concomitant aspirin and clopidogrel therapy, it was decided to provide continuous paravertebral blockade (PVB) with a local anesthetic/opioid combination.

The patient arrived in the operating room with a large-bore intravenous cannula and an arterial cannula in place. After application of standard monitors, she was then placed in a sitting position, and the paravertebral space at T8–T9 was identified. A loss-of-resistance technique was used, and the paravertebral space was found at a depth of 3.5 cm from the skin. An epidural catheter was advanced easily, and the test dose was negative. Fifteen milliliters of a 0.25% ropivacaine solution was administered via the catheter, and an infusion 0.2% of ropivacaine was started at 5 mL per hour.

A double-lumen endobronchial tube was placed, and the patient's left lung was deflated to facilitate surgical access and one-lung ventilation. Her SpO<sub>2</sub> decreased despite administration of 100% oxygen. Positive end-expiratory pressure was administered to the dependent lung, and continuous positive airway pressure was applied to the nondependent lung, resulting in improvement in SpO<sub>2</sub> (to 96%). A left lower lobectomy and mediastinal node dissection were performed uneventfully.

## CASE DISCUSSION

### Changes in Respiratory Function After Thoracotomy

Following thoracic surgery, characteristic respiratory abnormalities include a restrictive defect with severely reduced vital capacity and functional residual capacity. This decreased inspiratory capacity, limits the patient's ability to cough effectively, and increases the risk of atelectasis. Full return to preoperative values may not be seen for several weeks after surgery. Patients, such as the one presented in this case, who have pre-existing respiratory dysfunction and a long smoking history, are at greatest risk for postoperative pulmonary complications.

Both thoracic epidural analgesia (TEA) and PVB have been shown to preserve postoperative lung function. Some evidence suggests that the protective effect of PVB outweighs that of TEA. Figure 18.1 compares the proportionate preservation of lung function with different analgesic options.

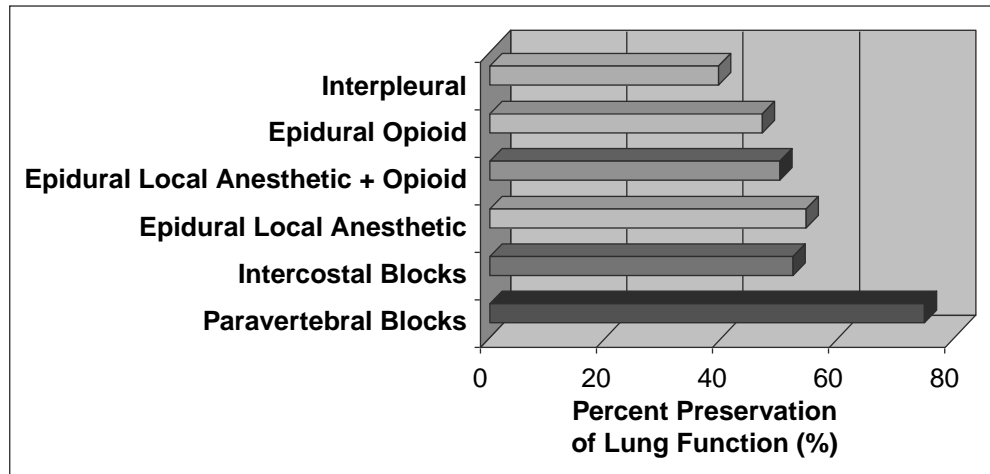
### Postthoracotomy Pain

Postthoracotomy pain is mediated by nociceptive output via three different nerve pathways: the intercostal, phrenic, and vagus nerves. Elevated catecholamine levels are observed, and the sympathetic nervous system is also activated. Effective pain control without respiratory depression is the major goal postoperatively and can be accomplished using either TEA or PVB.<sup>1–3</sup> It has been suggested that PVB may be unique because it can modulate the neuroendocrine stress response and abolish evoked potentials to thoracic dermatomal stimulation.

### TEA

Long considered the gold standard for the treatment of post-thoracotomy pain and still practiced exclusively in many institutions, TEA is an effective means of pain control in this setting. Unfortunately, TEA results in a bilateral sympathectomy, which can produce hypotension. In turn, this can require a reduction in the rate of the epidural infusion of local anesthetics and result in inadequate analgesia. Urinary retention can also occur. TEA has several limitations, with active anticoagulation considered an absolute rather than a relative contraindication. Because this patient had been treated with clopidogrel 3 days before surgery, she was still considered to have a potential impairment in hemostasis. The clinically accepted time for cessation of clopidogrel therapy before using a central neuraxial technique is 5 to 7 days, although





**Figure 18.1 • Comparison of Paravertebral Blockade and Thoracic Epidural Analgesia for the Treatment of Postthoracotomy Pain.** This figure demonstrates better efficacy of paravertebral blockade in preserving lung function after thoracotomy compared with a variety of other analgesia modalities. (Data from Richardson J, Sabanathan S, Shah R. Post-thoracotomy spirometric lung function: the effect of analgesia. A review. *J Cardiovasc Surg* 1999;40:445–456.)

this recommendation is largely empiric and based on the time required for full return of normal platelet function.

## PVB

First described in 1905, PVB remains underutilized. The paravertebral space is defined anterolaterally by the parietal pleura, posteriorly by the superior costotransverse ligaments, medially by the vertebrae, and superiorly and inferiorly by the heads of the ribs. The paravertebral space, like the epidural space, communicates both superiorly and inferiorly. Local anesthetic injected here will produce a unilateral somatic and sympathetic block.<sup>1,4</sup> Because this block is unilateral, paravertebral catheters generally produce less hypotension than TEA. Limited data suggest that PVB is more effective than TEA in preserving lung function after thoracotomy<sup>5</sup> (Fig. 18.2). Although the absolute contraindications for PVB are similar to those for TEA, anticoagulation is a relative contraindication. There are few vessels in the paravertebral space, and a paravertebral hematoma has fewer potential neurologic complications than a thoracic epidural hematoma.

## Technique for PVB

Paravertebral catheter placement involves a loss-of-resistance technique, similar to that of thoracic epidural catheter placement. With the patient in the sitting position, the desired thoracic level is identified. A mark should be made 2.5 cm lateral to the midpoint of the spinous process, and a 17-gauge Tuohy needle is advanced slowly until the transverse process is contacted (Fig. 18.3). The needle should then be redirected in a caudad fashion until a loss of resistance is felt, typically at 1 cm beyond the transverse process. The catheter should be threaded no more than 4 cm into the space for an adult and 2 to 3 cm for a child. This decreases the likelihood that

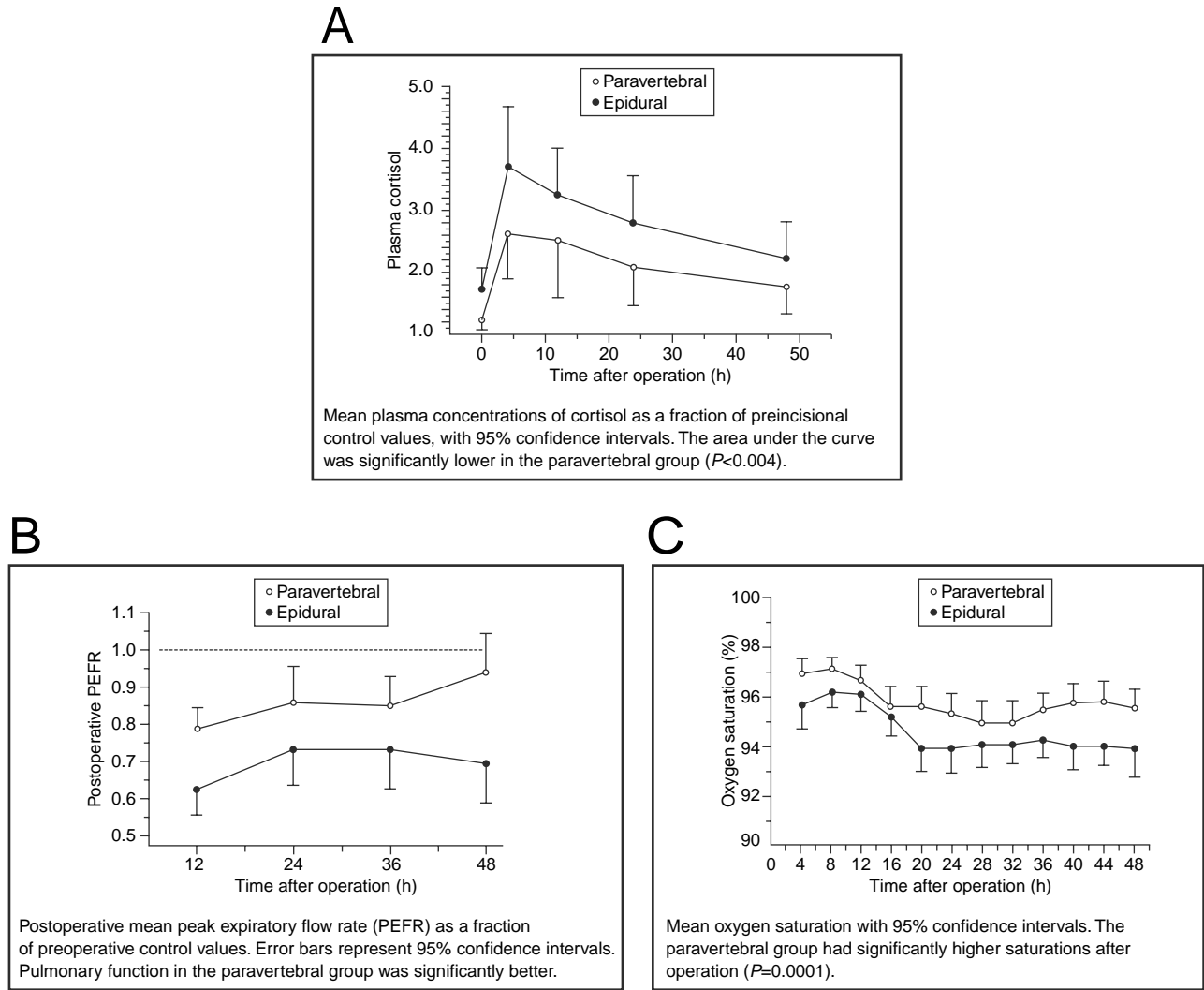
the catheter tip advances along the course of an intercostal nerve root. Test dosing is the same as for thoracic epidural placement.

## CONCLUSION

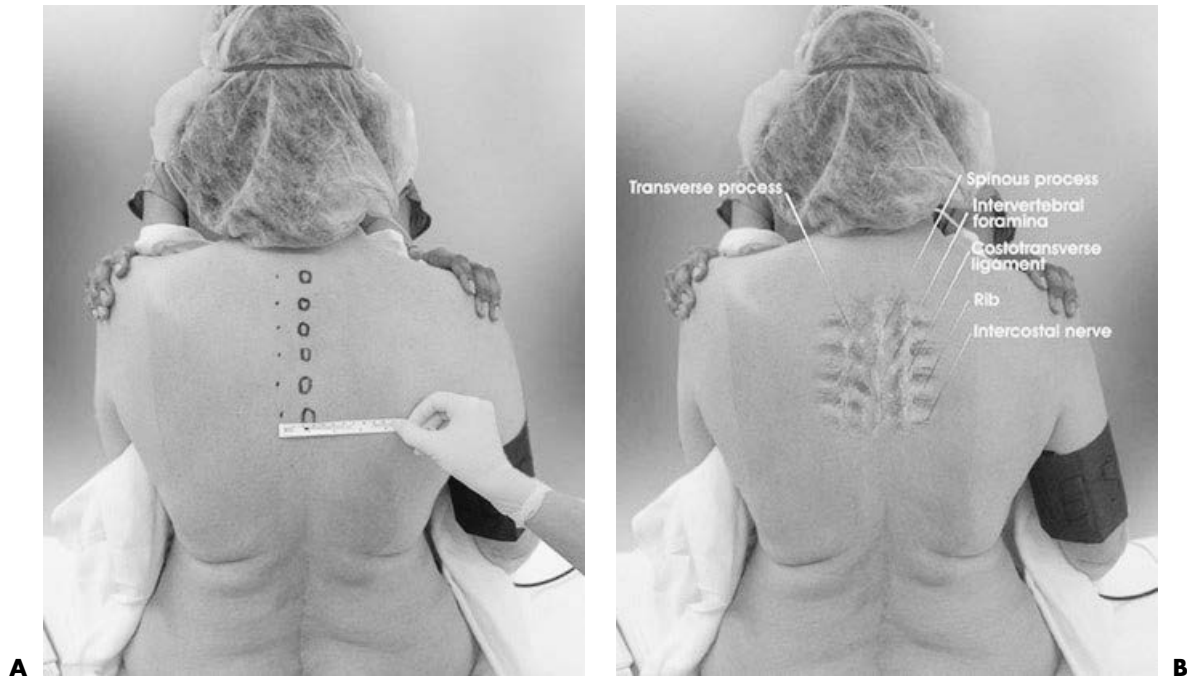
In summary, postthoracotomy pain is an important and often difficult problem to manage. TEA and PVB are both useful techniques for providing postoperative analgesia. The lesser incidence of hypotension, decreased stress response, unilateral blockade, and potentially better preserved pulmonary function than with TEA, make continuous PVB an attractive option, especially for patients with abnormal hemostatic function.

## KEY MESSAGES

1. Preoperative respiratory dysfunction may be associated with significant impairment of postoperative pulmonary function after thoracotomy and lung resection.
2. The etiology of postthoracotomy pain is multifactorial and involves both nociceptive and neuropathic pathways.
3. TEA or PVB can decrease respiratory depression associated with opioid use and can improve postoperative respiratory function.
4. Paravertebral catheter placement is technically straightforward and produces unilateral anesthesia and analgesia, compared with the bilateral effects of TEA.



**Figure 18.2 • Graph A Shows the Lower Cortisol Levels Seen with Paravertebral Blockade Compared with Thoracic Epidural Analgesia After Thoracotomy.** Graphs B and C show the improvement in spirometric values and oxygen saturation levels in patients treated with paravertebral blockade. (Reproduced with permission from Richardson J, Sabanathan S, Jones J, et al. A prospective, randomized comparison of preoperative and continuous balanced epidural or paravertebral bupivacaine on post-thoracotomy pain, pulmonary function and stress responses. *Br J Anaesth* 1999;83:387–392.)



**Figure 18.3 • Technique of Thoracic Paravertebral Blockade.** (From Hadzic A, Vloka JD. *Peripheral nerve blocks: principles and practice* New York: McGrawHill, 2004.)

## QUESTIONS

- Thoracic PVB:
  - Produces a bilateral thoracic sympathectomy
  - Produces more hypotension than thoracic epidural blockade
  - Is associated with improved postthoracotomy analgesia
  - Is inferior to intercostal blocks for postthoracotomy analgesia
  - Involves a noncontinuous space at the thoracic level

Answer: C

- Which of the following is the most important property of TEA?
  - Effective postoperative analgesia
  - Absence of urinary retention
  - Bilateral sympathectomy
  - Motor blockade
  - Alteration of cortisol levels

Answer: A

- Ideal performance of thoracic PVB includes:
  - Passage of catheters 6 cm into the paravertebral space in adults

- Palpation of the ipsilateral transverse process
- Needle insertion 2.5 cm lateral to the spinous process
- Performance in the lateral position
- Needle advancement 3 cm beyond the transverse process

Answer: C

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# Carotid Artery Stenosis

Christopher J. O'Connor

## CASE FORMAT: REFLECTION

An 82-year-old woman presented for carotid artery stenting (CAS) because of several recent transient ischemic attacks and a 70% restenosis of the left internal carotid artery. She had undergone a left carotid endarterectomy (CEA) 4 years previously. Her history was remarkable for hypertension, hypercholesterolemia, and coronary artery disease with prior stenting of her left anterior descending and circumflex coronary arteries 2 years ago. Her medications included metoprolol, lisinopril, simvastatin, clopidogrel, and aspirin. Her previous CEA had been performed under general anesthesia maintained using a remifentanyl infusion, nitrous oxide, and low concentrations of sevoflurane. She had recently presented with several episodes of amaurosis fugax. Carotid ultrasound and digital subtraction angiography studies confirmed a 70% restenosis of her left carotid artery. CAS was selected as the operative procedure to dilate and stent the stenotic vessel. Using intravenous (IV) sedation and infiltration with local anesthetic to expose her right femoral artery, carotid angioplasty and stenting were performed using a cerebral protection device to minimize distal embolization of atherosclerotic debris. After successful completion of CAS, the patient was transferred to the intensive care unit for monitoring with stable vital signs. Two hours after the procedure, she abruptly developed right-sided leg and arm weakness. A heparin infusion was started and continued for 48 hours; oral aspirin and clopidogrel therapy was maintained. Three days postoperatively, she underwent right groin exploration for drainage of a femoral hematoma and also required transfusion of two units of packed red blood cells. The patient was eventually discharged from the hospital to a nursing facility 10 days after CAS.

## CASE DISCUSSION

CEA is a well-validated procedure for managing symptomatic and asymptomatic carotid artery stenosis. Several studies have shown that CEA is superior to medical treatment for symptomatic patients with a stenosis of >60%, provided that centers performing CEA do so with a low rate of morbidity and mortality.<sup>1-3</sup> The Joint Committee of the Society for Vascular Surgery has determined that institutions performing this surgery should have a combined stroke mortality rate

of <3% for asymptomatic patients, <5% for symptomatic patients, and <7% for those with a prior stroke. CAS and transluminal balloon angioplasty of the carotid artery was introduced as a minimally invasive approach to carotid stenosis that would avoid the risks associated with surgery and general anesthesia in high-risk patients. CAS avoids a neck incision that can lead to cranial nerve injuries or postoperative wound infections. However, the efficacy of CAS versus CEA in decreasing subsequent neurologic morbidity had not been determined when CAS was introduced. Several recent studies and meta-analyses<sup>4-7</sup> indicate that CEA can be performed safely with a lesser risk (compared with CAS) of stroke or death at 3 and 6 months postoperatively. Many surgeons consider CEA to be the “gold standard” for the treatment of carotid stenosis in both low- and high-risk patients.

## CEA

CEA entails a longitudinal arteriotomy of the involved vessel after cross clamping of the internal carotid artery. The plaque is removed by cephalad extension of the endarterectomy plane until all of the plaque has been removed. To decrease the incidence of restenosis, many surgeons perform CEA (and several have shown superior results) with patch angioplasty. Either a piece of autologous vein or synthetic material is used to close the arteriotomy. Patch angioplasty significantly decreases the risk of perioperative stroke or death, the risk of perioperative restenosis, and the long-term risk of restenosis.

Anesthetic goals during CEA are to prevent stroke and perioperative myocardial infarction (MI) by optimizing intraoperative cerebral and myocardial perfusion. Although adequate cerebral perfusion can be maintained during the period of carotid clamping from the contralateral carotid artery via the Circle of Willis, 10% to 15% of the time, clamping will lead to symptomatic hemispheric ischemia.

The optimal anesthetic for CEA has yet to be determined (Table 19.1). The use of regional anesthesia—comprising deep or superficial cervical plexus block, local anesthetic infiltration, or a combination of these—has been advocated to decrease the incidence of perioperative MI, maintain intraoperative hemodynamic stability, reduce the duration of hospitalization, and reduce costs. However, none of these contentions has ever been firmly established in large-scale, randomized trials. It has been suggested that the response of the awake patient during carotid clamping represents the “gold standard” for neurologic monitoring in that patients can reliably display signs of cerebral ischemia during the period of carotid clamping. Although this may be true, it has yet to be borne out by any evidence base

**TABLE 19.1** A Comparison of the Advantages and Disadvantages of Regional Versus General Anesthesia for Carotid Endarterectomy

Technique	Advantages	Disadvantages
<b>Regional</b>	Less intraoperative hypotension Simple nerve block Intubation not required  Sensitive neurologic monitor  Avoids postoperative somnolence of GA  Shorter hospitalization, lower cost, fewer CV complications  Provides postoperative analgesia	More intraoperative hypertension Unfamiliarity for surgical team Challenging airway control if GA needed  Sedation may obscure neurologic monitoring  Patient discomfort if cerebral ischemia develops  Sedation-induced hypoxemia may increase cerebral ischemia  Need to convert to GA
<b>General</b>	Reliable airway control Secure control of PaCO <sub>2</sub> , PaO <sub>2</sub>  Possible neuroprotective effects of anesthetics	Intubation required More intraoperative hemodynamic changes  Delayed emergence may obscure diagnosis of new cerebral event

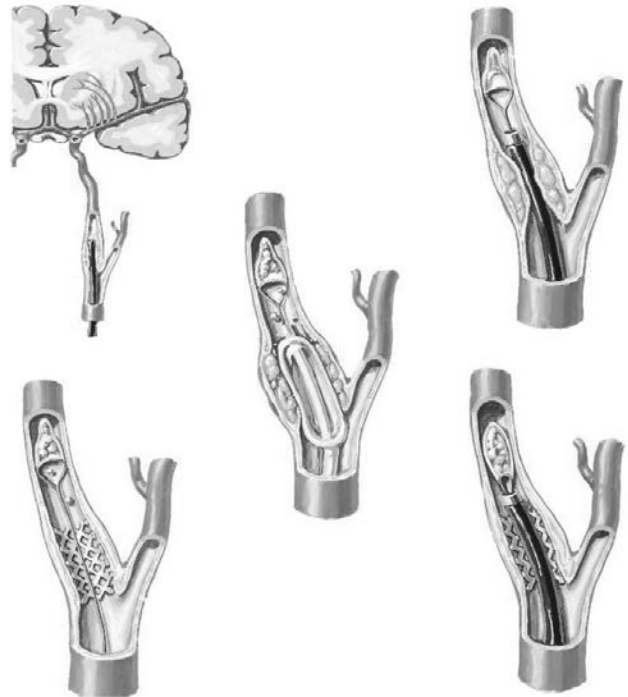
CV, cardiovascular; GA, general anesthesia.

data. In addition, technical factors may limit the use of regional anesthesia. These include the presence of a short, obese neck; a high carotid bifurcation or tortuous arteries; and patients who are anxious or agitated. In the United States, more than 90% of CEAs are performed on patients under general anesthesia. It is likely that until the superiority of one technique over another has been established, most clinicians will continue to choose general anesthesia for CEA.

A variety of monitors/methods have been used to assess the adequacy of cerebral perfusion during CEA. These include electroencephalography or somatosensory-evoked potentials, transcranial Doppler, and stump pressure measurement. None of these methods is infallible, and they cannot reliably detect intraoperative cerebral ischemia or predict postoperative stroke. Stump pressure measurements and cerebral oximetry yield low rates of sensitivity and specificity for the detection of cerebral ischemia. Transcranial Doppler monitoring is technically more demanding (e.g., maintenance of angle of insonation) and inconsistent in acquiring blood flow signals. However, 16-lead electroencephalography monitoring is a reliable and valid neurologic monitor during CEA. Ultimately, the choice of intraoperative monitor may be less critical than surgical factors, because cerebral ischemia during the period of carotid clamping is an uncommon cause of perioperative stroke. Most neurologic injuries occur secondary to perioperative thromboembolic events (as in the case described).

### CAS

CAS (Fig. 19.1) was originally introduced as a minimally invasive approach to managing carotid stenosis that would avoid

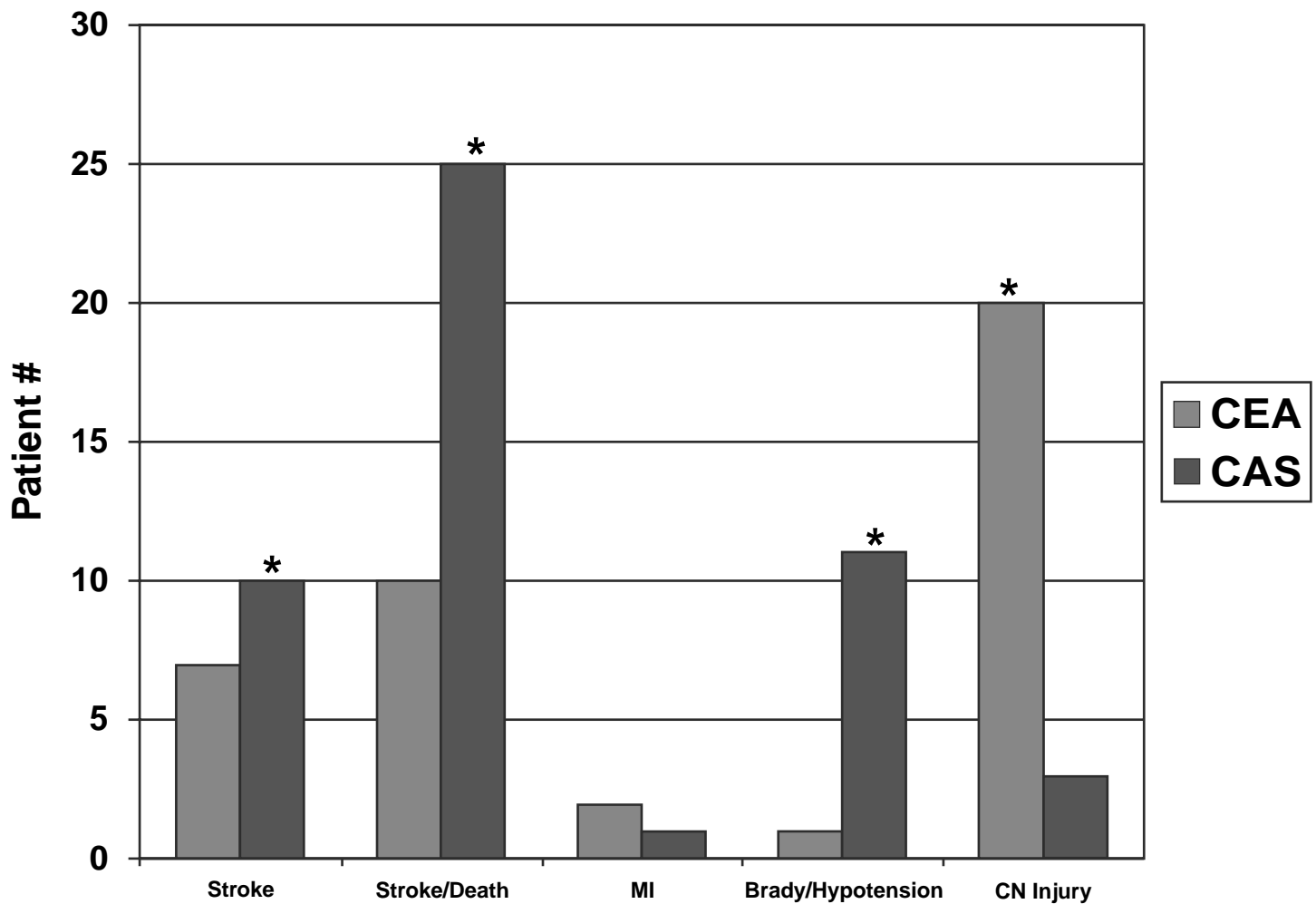


**Figure 19.1 • The Technique of Carotid Artery Angioplasty and Stenting.**

the risks of surgery and general anesthesia in high-risk patients. CAS is currently approved only for patients in clinical trials evaluating the efficacy of CAS. It was advocated for the high-risk patient with clinically significant cardiac (severe ischemic disease or significant congestive heart failure) or pulmonary disease, very advanced patient age (>80 years), or those with certain anatomic factors that make CEA more difficult. However, current evidence indicates that CAS has a greater 30-day death or stroke rate and greater 1-year stroke and death rates compared with CEA (Fig. 19.2). In addition, CAS appears superior only in the setting of conditions that render surgery technically difficult, such as restenosis after prior CEA (as in the patient in this case), prior radical neck surgery, previous neck radiation, and in selected patients with severe concurrent cardiopulmonary disease. Currently, carotid

stenting should only be performed in high-volume, specialized centers with experience in CAS, where stenting and angioplasty can be used in selected individuals with specific lesions amenable only to nonoperative treatment. One advantage of CAS compared with CEA is the lesser incidence of cranial nerve injuries (although local complications such as groin hematomas are more common with CAS).

Anesthesia for CAS is usually performed with local anesthetic infiltration, with or without monitored anesthesia care and sedation. Bradycardia can occur at balloon dilation of the carotid artery; this can typically be managed with balloon deflation and administration of IV anticholinergic agents. The use of cerebral protection devices—either umbrellas or balloon devices to trap embolic material—has lessened the incidence of procedural-related cerebral ischemic events.



**Figure 19.2 • Data Comparing Outcomes Between CAS and CEA.** It is apparent that the incidence of stroke or combined stroke and death are lower in patients undergoing CEA compared with CAS. It is also clear that the incidence of myocardial infarction—expected to be lower with the less-invasive approach of CAS—was no different between the two groups. In contrast, hypotension and bradycardia were higher in the CAS group. Cranial nerve injuries were higher in the CEA group, as expected. CAS, carotid artery stenting; CEA, carotid endarterectomy; CN, cranial nerve; MI, myocardial infarction. \*  $p < 0.05$ . (Data from Mas JL, Chatellier G, Beyssen B, et al. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med* 2006;355:1660–1671.)

**KEY MESSAGES**

1. Overall, CEA appears to be associated with a lesser risk of stroke, MI, and death when compared with CAS.
2. Based on currently available evidence, CAS should be reserved for high-risk patients with severe concomitant cardiac disease or anatomic conditions that render surgery technically difficult, such as restenosis after prior CEA, prior radical neck surgery, or previous radiation to the neck.
3. CEA is commonly performed on patients with general anesthesia, although many patients can be managed safely with IV sedation and combined superficial/deep cervical plexus blocks. In contrast, CAS is primarily performed on patients who receive IV sedation and local infiltration with a local anesthetic.

**QUESTIONS**

1. As compared with CEA, CAS is most often associated with:
  - A. Lower incidence of local complications
  - B. More frequent nonfatal strokes
  - C. Intraoperative hypotension
  - D. Lower rates of perioperative MI
  - E. Fewer cranial nerve injuries

Answer: B
2. Regional anesthesia for CEA:
  - A. Is associated with higher hospital costs than general anesthesia
  - B. Results in lower perioperative stroke rates than general anesthesia

- C. Is best achieved with a superficial cervical plexus block
- D. Has a high conversion rate to general anesthesia
- E. Allows for communication with the patient during carotid occlusion

Answer: E

3. Which of the following is most likely to detect cerebral ischemia during carotid occlusion?
  - A. Stump pressure measurement
  - B. Cerebral oximetry
  - C. Sixteen-lead electroencephalography analysis
  - D. Transjugular venous oxygen saturation
  - E. Motor-evoked potentials

Answer: C

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# Postpneumonectomy Pulmonary Edema

Nanhi Mitter

## CASE FORMAT: STEP BY STEP

A 72-year-old, 5'8", 60-kg man with a history of hypertension, benign prostatic hypertrophy, and hyperlipidemia presented with progressive dyspnea, cough, and recent (2-month) weight loss of 7 kg. Bronchoscopy and mediastinoscopy confirmed the diagnosis of non-small cell carcinoma, and he was scheduled to undergo a right pneumonectomy.

The patient was currently smoking two packs of cigarettes per day and had an 80-pack year smoking history. His pulmonary function tests revealed a decreased forced expiratory volume/forced vital capacity (60% predicted) and a reversible component to his bronchospasm. His medications included fluticasone/salmeterol, aspirin, simvastatin, metoprolol, and amlodipine. He was not using home oxygen therapy.

On preoperative evaluation, the patient seemed comfortable with a normal airway examination and diminished breath sounds over the right lung field. His vital signs were as follows: blood pressure, 150/84 mm Hg; heart rate, 70 beats per minute; respiratory rate, 20 breaths per minute; and SpO<sub>2</sub>, 90% to 94% on room air. His room air blood gas revealed pH, 7.34; pCO<sub>2</sub>, 56 mm Hg, and pO<sub>2</sub>, 98 mm Hg. The patient's preoperative cardiac evaluation revealed left ventricular hypertrophy on electrocardiogram and normal left ventricular ejection fraction on echocardiography. He had not experienced chest pain but described fatigue and shortness of breath on minimal exertion, which he attributed to his lung disease. Preoperative investigations revealed a hemoglobin concentration of 17 g/dL (all other parameters were normal).

After a 16-gauge intravenous and an arterial catheter were inserted, the patient was taken to the operating room where an epidural catheter was introduced at the T8 level. After a test dose was administered via the epidural catheter, two 5-mL increments of 2% lidocaine with epinephrine (1:200,000) were administered. An infusion of bupivacaine (0.125%) and fentanyl (10 mcg/mL) was commenced and continued throughout the case. The patient's trachea was intubated using a left-sided 37 F double-lumen tube (DLT). A central venous catheter was inserted into the right internal jugular vein. Upon institution of one-lung ventilation (OLV), the patient's oxygen saturation decreased from 99% to 92% over 15 minutes.

## What is the appropriate initial response to the decrease in SpO<sub>2</sub>?

Possible etiologies of hypoxemia during OLV include malposition of the DLT, bronchospasm, low FiO<sub>2</sub>, dependent lung atelectasis, and secretions. The anesthesiologist should confirm the patient is receiving an FiO<sub>2</sub> of 1.0 and establish that the DLT is correctly positioned. It would be reasonable to apply suction to the ventilated lung and administer a bronchodilator such as albuterol. CPAP to the non-ventilated lung would be the next step to improve oxygenation.

Following these maneuvers, the patient's SpO<sub>2</sub> increased to 96%. Surgery proceeded, and while the surgeon was dissecting the pulmonary artery, severe hemorrhage ensued, and an acute blood loss of 2 liters (over 5 minutes) was observed. Two units of packed red blood cells were administered, and the arterial blood gas revealed a metabolic acidosis (pH = 7.30) with a hemoglobin level of 7 g/dL. The patient's central venous pressure was 5 mm Hg, blood pressure was 100/50 mm Hg, and his heart rate measured 110 beats per minute.

## Are patients undergoing pneumonectomy at risk of "fluid overload"?

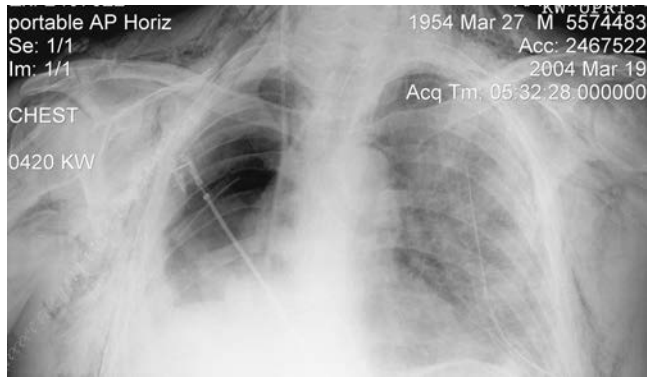
Excess intraoperative fluids may play a role in the development of post-pneumonectomy pulmonary edema. In the face of global hypoperfusion, however, as evidenced by metabolic acidosis and the observed hemodynamic instability, fluid resuscitation takes priority.

The anesthesiologist administered another two units of packed red blood cells. The surgeon controlled the bleeding, and 2 hours later, the right lung was resected, and the patient's chest was closed. The total blood loss was estimated to be 3 liters and the results of the patient's blood gas analysis and hemoglobin concentration had normalized. He had received a total of 4 units of packed red blood cells and 1 liter of crystalloid; his vital signs were also normal. Upon auscultation of his left lung, mild expiratory wheeze was audible.

After complete reversal of neuromuscular blockade and administration of albuterol (by metered dose inhaler with extension), the patient's trachea was extubated, and 40% oxygen was administered by Venturi face mask. The patient was admitted to the ICU postoperatively; his chest radiograph (CXR) upon arrival revealed mild pulmonary congestion in his left lung field and an absent right lung.

The patient's ICU course was uneventful. On the second postoperative day, he was transferred to the ward but experienced mild dyspnea 1 day later. He continued to complain of progressive dyspnea, and his SpO<sub>2</sub> gradually decreased from





**Figure 20.1** • In the patient's postoperative day 3 chest x-ray, note the pulmonary edema pattern in the left lung and the normal cardiac silhouette, suggesting an acute lung injury pattern.

97% on a 50% oxygen face mask to 90% over the course of his third postoperative day. A CXR revealed pulmonary edema in the left lung field (Fig. 20.1). Blood gas analysis revealed PaO<sub>2</sub> to be 60 mm Hg.

### What are the risk factors for postoperative pulmonary edema?

The risk factors for postpneumonectomy pulmonary edema are listed in Table 20.1.<sup>1-6</sup>

### What are the options for ventilatory management of this patient?

At this point, the options for ventilatory management include noninvasive ventilation, transfer to the ICU for closer monitoring, or immediate tracheal intubation and transfer to the ICU.

In light of the pneumonectomy, fluid administration, CXR, and arterial blood gas results, it was decided to reintubate the patient's trachea and transfer him to the ICU. This decision was made to avoid further hypoxemia given that the clinical picture was consistent with hydrostatic pulmonary edema or acute lung injury. Over the next few hours, the patient's oxygenation improved, and he was successfully weaned from the ventilator on postoperative day 5. The remainder of his postoperative course was uneventful.

**TABLE 20.1** Predictors of Postpneumonectomy Pulmonary Complications

1. Right pneumonectomy
2. Excessive perioperative fluid administration
3. Increased intraoperative ventilation pressures
4. Preoperative alcohol abuse
5. Decreased postoperative predicted DLCO (diffusing capacity of the lung)
6. Radiation therapy

### KEY MESSAGES

1. Patients undergoing pneumonectomy are at risk for postoperative pulmonary dysfunction from interstitial edema, atelectasis, and restrictive respiratory patterns caused by inadequate analgesia.
2. Risk factors for postpneumonectomy pulmonary edema include excess intraoperative fluid administration, prior chest irradiation, right pneumonectomy, and possibly preoperative alcohol use and high intraoperative ventilatory pressures.
3. The management of postpneumonectomy pulmonary edema is largely supportive, including supplementary oxygen, mechanical ventilatory support if necessary, diuresis, and aggressive pulmonary toilet.

### QUESTIONS

1. Which of the following statements are true?
  - A. Patients undergoing a right pneumonectomy have no added risk for postoperative pulmonary edema.
  - B. All patients undergoing a pneumonectomy should have pulmonary function tests completed preoperatively.
  - C. Hypoxic pulmonary vasoconstriction should be maximized in the dependent lung.
  - D. All patients should be ventilated with high lung volumes (10–12 mL/kg). This is the only way to ensure that atelectasis will not develop.
  - E. None of the above

Answer: B

2. Which of the following statements is false regarding management of hypoxemia during OLV?
  - A. The bronchial cuff of the DLT when visualized with a fiberoptic bronchoscope should be about 1 cm above the carina.
  - B. During OLV, positive end-expiratory pressure to the dependent, ventilated lung may worsen the shunt.
  - C. During OLV, constant positive airway pressure to the nondependent, nonventilated lung may improve oxygenation.
  - D. High tidal volumes may injure alveoli in the ventilated lung.
  - E. An FiO<sub>2</sub> of 1.0 should be used.

Answer: A

3. Which of the following are risk factors for the development of postpneumonectomy pulmonary edema?
  - A. Right pneumonectomy
  - B. A history of breast cancer
  - C. Large volumes of intraoperative fluid
  - D. A and C
  - E. None of the above

Answer: D

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# Perioperative Antiplatelet Therapy

Nanhi Mitter

## CASE FORMAT: REFLECTION

A 62-year-old female with a history of coronary artery disease, hyperlipidemia, and hypertension presented with vaginal bleeding and was scheduled for a total abdominal hysterectomy and bilateral salpingo-oophorectomy. Unfortunately, 3 days before she was due to undergo this operation, she experienced substernal chest pain radiating to her jaw. She was taken to the emergency department where her electrocardiogram readings (Fig. 21.1) and cardiac enzymes were consistent with an ST-segment elevation myocardial infarction (MI). She underwent emergency coronary angiography, which revealed 99% occlusion of the left circumflex artery. An angioplasty was performed, a bare metal stent (BMS) was placed across the lesion, and normal flow was re-established. She was admitted to the coronary care unit, and after an uneventful recovery was discharged home 5 days later.

The patient's total abdominal hysterectomy and bilateral salpingo-oophorectomy had been canceled and was rescheduled for 4 weeks after her ST-segment elevation MI. On preoperative evaluation for the re-scheduled procedure, she was noted to be taking metoprolol, hydrochlorothiazide, simvastatin, and aspirin. She had stopped taking clopidogrel 7 days previously but had continued to take aspirin. She had stopped smoking 3 years previously, and her alcohol consumption was minimal. With the exception of hemoglobin concentration 8.9 g/dL, all of her laboratory values were within normal limits. Since her ST-segment elevation MI, she had been asymptomatic and had been able to walk on a treadmill without difficulty. She appeared nervous but otherwise healthy. The patient's vital signs were as follows: temperature, 37.0°C; blood pressure, 120/71 mm Hg; heart rate, 62 beats per minute; respiratory rate, 18 beats per minute; and room air oxygen saturation, 99%. Her physical examination was unremarkable, and the upper airway was evaluated as normal.

After standard ASA monitors were applied and the arterial and venous cannulae were inserted, anesthesia was induced, and the patient's trachea was intubated uneventfully. A triple-lumen catheter was inserted in her right internal jugular vein, and her central venous pressure (CVP) was monitored continuously. Two hours into the procedure, blood loss was estimated to be 1 liter, the patient became tachycardic and hypotensive, and her CVP was 3 mm Hg. Arterial blood gas analysis revealed metabolic acidosis, and the patient's hemoglobin concentration was 6.6 g/dL. Two units of

packed red blood cells and 50 mL of 8.4% sodium bicarbonate were administered rapidly, and hyperventilation was instituted. Despite aggressive fluid resuscitation, the patient remained hypotensive (mean arterial pressure 40–45 mm Hg) with a CVP of 3 mm Hg. A transesophageal echocardiographic probe was inserted and revealed no regional wall motion abnormalities. After transfusion of two further units of packed red blood cells, the patient's hemodynamic parameters normalized. The surgery continued without further incident. At the end of the procedure, her CVP was 11 mm Hg. A repeat arterial blood gas analysis revealed a normal pH and a hemoglobin level of 11g/dL. The patient's trachea was extubated, and she was transferred to the ICU where a cardiac evaluation was normal.

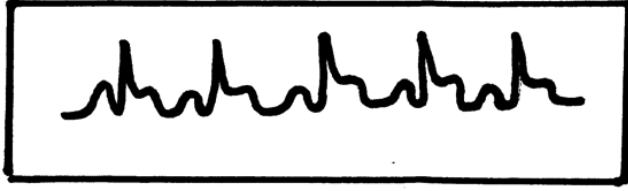
## CASE DISCUSSION

Percutaneous coronary interventions (PCI) generally should not be performed as a preoperative step to prevent adverse cardiovascular events for patients undergoing noncardiac surgery unless they present with an acute coronary syndrome. Patients who present with an acute coronary syndrome and who require subsequent noncardiac surgery require special evaluation and manipulation of their medical therapy.<sup>1</sup> The type of intervention—percutaneous transcatheter angioplasty versus coronary artery stenting—should be planned considering the choice of dual-antiplatelet therapy (DAT), risk of bleeding, and the nature and timing of surgery.

Using the guidelines outlined in Table 21.1 will help with planning for surgery.

Current recommendations regarding DAT include the use of aspirin and a thienopyridine agent. DAT is initiated because upon balloon inflation or stent deployment, the endothelium of the coronary artery is denuded. Normally, the endothelium functions to inhibit platelet aggregation along the vessel wall. Without the endothelium present, pharmacologic agents such as aspirin and a thienopyridine agent must provide for the platelet inhibitory function until the endothelium resumes this role.

In the setting of balloon angioplasty (BA) and BMS, the endothelium develops after 4 to 6 weeks; hence DAT is no longer necessary and is subsequently discontinued.<sup>2</sup> After a period of time, however, late stent restenosis of the BMS can lead to MI or even death, and therefore, drug-eluting stents (DES) have become widely used. There are two types of DES—the sirolimus-eluting stent and the paclitaxel-eluting



**Figure 21.1** • The patient's electrocardiogram reading reveals an ST-segment elevation myocardial infarction.

stent. These stents are impregnated with chemotactic agents that help to prevent re-endothelialization that leads to late stent restenosis. Because these stents prevent re-endothelialization, DAT is mandated to prevent acute thrombosis of the stent for longer periods of time compared with BMS or balloon angioplasty.

In patients who have undergone balloon angioplasty, performing noncardiac surgery within the first 2 weeks may be unsafe because of residual injury from recent vessel manipulation. Performing surgery between 2 to 4 weeks is ideal because of theoretical vessel healing and the low risk of restenosis at the site, which is most common after 8 weeks. Patients should be treated with DAT for 4 to 6 weeks.<sup>2-4</sup>

In patients undergoing stenting with BMS, the risk of acute thrombosis is greatest in the first 2 weeks, and the risk for restenosis is greatest >12 weeks. Therefore, the ideal time for noncardiac surgery after BMS is 4 to 6 weeks, as it is rare for thrombosis to occur during this interval because of at least partial endothelialization of the BMS. DAT should be continued for 1 month when BMS are used and in some cases longer.<sup>4</sup>

In patients undergoing stenting with DES, the current recommendation is to delay elective surgery until the patient has completed the appropriate course of DAT. In the event of urgent or emergent surgery when the thienopyridine therapy must be discontinued, then, if at all possible, the aspirin should be continued perioperatively, and the thienopyridine therapy should be restarted as soon as possible.

In this case, the patient had a BMS placed and underwent surgery after 4 weeks. Although this is the ideal time to

perform surgery in patients with BMS, the risk of acute stent thrombosis (albeit rare, <0.1% in most case series) and reinfarction is present.<sup>1,5</sup>

Invasive monitoring such as a transesophageal echocardiogram can be helpful in these patients to differentiate between intrinsic cardiac etiology (i.e., in-stent restenosis manifesting as regional wall motion abnormalities) versus extrinsic factors that may lead to hemodynamic instability (i.e., hypovolemia secondary to acute blood loss or to bowel preparation). High-risk patients can be managed by optimizing the myocardial oxygen supply/demand ratio. Methods to achieve this goal include but are not limited to avoiding tachycardia, providing adequate analgesia in the preoperative setting, optimizing oxygenation and ventilation, avoiding alkalosis and acidosis, avoiding anemia, aggressive fluid resuscitation, perioperative  $\beta$ -blockade, and statin use. Finally, postoperative management may include ICU admission and close follow-up.

#### KEY MESSAGES

1. Preoperative management of a patient who has had a recent acute MI but needs urgent noncardiac surgery requires special consideration with respect to anticoagulation and the type of revascularization procedure to be performed.
2. Antiplatelet therapy is necessary in patients undergoing PCI because of denuding of the endothelium from balloon deployment or the device used. The American College of Cardiology and the American Heart Association recommend varying durations for DAT depending on the type of coronary intervention.
3. For patients who have had a DES placed, continuation of both clopidogrel and aspirin in the perioperative period is recommended. If clopidogrel needs to be stopped, aspirin should be continued throughout the perioperative period.

**TABLE 21.1** Recommendations Regarding Time Frame for Surgical Intervention After Revascularization

Mode of Revascularization	Unsafe	Safe Period	Unsafe
BA	<2 weeks	>2 weeks	
BMS	<4–6 weeks	4–6 weeks	>12 weeks
DES	<1 year	After 1 year	

This table demonstrates “safe” and “unsafe” time periods for patients undergoing elective noncardiac surgery after a revascularization procedure. The decision regarding timing of surgery should be ultimately made by the anesthesiologist, surgeon, cardiologist, internist, and patient involved. Data based on the American College of Cardiology/American Heart Association 2007 guidelines.

BA, balloon angioplasty; BMS, bare metal stent; DES, drug-eluting stent.

## QUESTIONS

1. Which of the following drug combinations are used as DAT for patients undergoing PCI?
  - A. Aspirin and clopidogrel
  - B. Lovenox and clopidogrel
  - C. Coumadin and clopidogrel
  - D. Coumadin and aspirin

Answer: A

2. Which of the following is a true statement regarding antiplatelet therapy (AT) in patients who have undergone PCI?
  - A. The patients are placed on AT because they are at risk for stroke after PCI.
  - B. In patients undergoing PCI with DES, only 3 months of aspirin are necessary for AT.
  - C. Patients need AT after PCI because in the process of balloon or stent deployment, the endothelium is denuded—the normal endothelium is necessary to prevent platelet aggregation.
  - D. Patients only need AT if they are having a stent placed.

Answer: C

3. Which of the following statements is/are correct?
  - A. All patients who have symptomatic coronary artery disease should undergo revascularization just so that they can have their elective surgery.

- B. It is recommended to wait 4 to 6 weeks after patients have had a BMS placed before proceeding with surgery.
- C. Only 6 weeks of DAT are necessary for patients who have had placement of a DES.
- D. Elective surgery can be performed without incident in patients after BA within the first 2 weeks of the PCI.

Answer: B

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# Intraoperative Blood Conservation Strategies

W. Christopher Croley

## CASE FORMAT: REFLECTION

A 14-year-old, 50-kg female presented for spine surgery. She was an otherwise healthy teenager who had undergone previous back surgery for scoliosis. She reported taking ibuprofen “occasionally” for back pain. Physical examination was unremarkable except for severe thoracic scoliosis. Her preoperative hemoglobin concentration was 13 g/dL, and all other laboratory values were within normal limits.

The patient was scheduled to undergo an estimated 6-hour procedure in the prone position. Her parents were present in the preoperative holding area and expressed their concern with her preoperative hemoglobin concentration and the possible need for a blood transfusion perioperatively. Several strategies were discussed with the patient and her parents.

A decision was made jointly to use acute normovolemic hemodilution before starting the case, cell saver intraoperatively, and blood transfusion only if signs of decreased oxygen carrying capacity were demonstrated.

Two 16-gauge peripheral intravenous catheters were inserted while the patient was in the holding area. In the operating room, standard ASA monitors were placed, and general anesthesia was induced with sufentanil (1 mcg/kg), propofol (2 mg/kg), and rocuronium (0.6 mg/kg). After induction of general anesthesia, tracheal intubation was readily accomplished with a 7.0-mm oral endotracheal tube. An 18-gauge right radial arterial line was inserted for blood pressure monitoring, blood sampling, and to facilitate normovolemic hemodilution. Anesthesia was maintained with a sufentanil infusion at 0.3 mcg/kg per hour, sevoflurane (inspired concentration 1.5%–2%), and a 50:50 mixture of nitrous oxide/oxygen. Motor-evoked potentials were monitored; therefore, no additional neuromuscular blocking agent was used.

Utilizing strict aseptic technique, 500 mL of blood was collected using the arterial cannula in a citrate-phosphate-dextrose containing bag. Simultaneously, 500 mL of 6% hetastarch was administered intravenously. The patient was hemodynamically stable throughout the procedure. Approximately 4.5 hours into the surgery, the estimated blood loss was 900 mL, and the surgeon was starting to close. Using the products of cell salvage collected intraoperatively, 300 mL was administered. The patient’s trachea was extubated at the end of the procedure, and she was transferred to the recovery room with stable vital signs. Her postoperative hemoglobin concentration was 10 g/dL. She

was discharged home on the third postoperative day, at which time her hemoglobin concentration was 9 g/dL. The patient and her family were very happy that she did not require allogeneic blood during her hospitalization.

Infectious risks, immunosuppression, limited availability, and acquisition costs are legitimate concerns of clinicians responsible for transfusion of blood products. These concerns cause those responsible for perioperative care to continually evaluate and implement therapies to reduce perioperative blood loss and thereby minimize the need for allogeneic blood transfusion. Numerous mechanical, pharmacologic, and physiologic strategies have been identified to decrease blood transfusion.<sup>1–5</sup> Several of these strategies can be used in combination in a single case.

Preoperative autologous blood donation (ABD) is one technique that can be used.<sup>6,7</sup> This procedure entails patients donating their own blood, which is then stored for transfusion at a later date. This process must be initiated several weeks in advance of anticipated need to allow time for restoration of intravascular volume as well as preparation of the donated blood. Patients can donate every 72 hours, and the last donation should be at least 72 hours before a scheduled procedure. ABD is contraindicated in patients with anemia (hemoglobin <11 g/dL or hematocrit levels <33% before each donation). Problems associated with this technique include mislabeling blood products, bacterial contamination of stored units, and the costs associated with collection and administration. Costs associated with preoperative ABD can be 50% to 70% greater than similar techniques of acute normovolemic hemodilution and cell salvage (Table 22.1).

Acute normovolemic hemodilution (ANH) is the process of removing whole blood while simultaneously infusing crystalloid or colloid fluid to maintain intravascular volume. This is an effective, low-cost means of intraoperative blood conservation that is underutilized. Blood is collected in citrate-phosphate-dextrose-containing bags at the beginning of the procedure and stored in the operating room, at room temperature, for up to 8 hours. Collection bags are numbered by the order in which they were collected and are then transfused in the reverse order. This means the first bag collected, which (theoretically at least) has a greater red blood cell mass and greater concentration of clotting factors, is transfused last. Because this product is not collected and stored off-site, risks of clerical errors and processing of the blood are greatly reduced. ANH is also a more cost-effective method of decreasing perioperative blood transfusion requirements. Platelets and clotting factors are usually

**TABLE 22.1** Contraindications to Autologous Blood Donation

<ul style="list-style-type: none"> <li>• Anemia (hemoglobin &lt;11 g/dL)</li> <li>• Infection or risk of bacteremia</li> <li>• Angina</li> <li>• Recent myocardial infarction</li> <li>• Uncontrolled seizure disorders</li> </ul>
--

well preserved with this method because the blood is stored at room temperature and then transfused within a relatively short time. Relatively few studies have examined the practice of ANH. A small number of prospective, randomized studies have been completed and represent ANH as equivalent to preoperative autologous donation in reducing the need for allogeneic blood transfusions.

Cell salvage and reinfusion is another commonly used method for autologous blood procurement and can be done intraoperatively or postoperatively. Cell salvage techniques involve devices that collect blood as it is lost and facilitate its subsequent retransfusion. Red blood cells collected in this manner are commonly filtered through a microaggregate filter before transfusion to remove tissue debris and blood clots. The function of red blood cells from salvage techniques appears to be similar to that of allogeneic red blood cells. This technique cannot be used if topical procoagulants (e.g., topical thrombin) are present in the surgical field from which the blood is being recovered. Salvaged blood often undergoes a washing procedure using saline solutions to remove some inflammatory mediators (e.g., cytokines). Unwashed salvaged blood has a greater incidence of hypotension, hyperthermia, and pulmonary edema when reinfused than washed blood. Other risks associated with cell salvage include air emboli, infection, and coagulation derangements.

Induced hypotension is an anesthetic technique that can be used to minimize intraoperative blood loss.<sup>8</sup> This technique has been well described, primarily in the orthopaedic literature, where it has been shown that blood loss can be reduced by 30% to 50% when using a hypotensive or regional (spinal or epidural) technique. Induced hypotension involves lowering the mean arterial pressure to 50–55 mm Hg, using either sympathectomy associated with neuraxial anesthesia or vasoactive agents (e.g., esmolol, nicardipine, nitroprusside). Hypoperfusion is the obvious concern when deliberately lessening the patient’s blood pressure. This technique should be used cautiously in patients with altered autoregulatory mechanisms (e.g., hypertension) and those susceptible to ischemic complications (e.g., coronary artery disease, renal insufficiency, diabetes). It should also be noted that induced hypotension and ANH are sometimes used in combination. Using this combination increases the risk of decreased oxygen delivery.

Pharmacologic methods that can decrease the need for perioperative blood transfusion (but not necessarily intraoperative blood loss) include preoperative administration of erythropoietin and/or intraoperative administration of antifibrinolytic agents such as aprotinin, ε-aminocaproic acid, or tranexamic acid.<sup>9</sup> Erythropoietin is a glycoprotein hormone that stimulates red blood cell production. Numerous studies of or-

**TABLE 22.2** Overview of Pharmacologic Agents

<b>Antifibrinolytic Agents</b>	Aminocaproic acid Tranexamic acid
<b>Topical Agents</b>	Thrombin Gelatin sponges Fibrin
<b>Procoagulant Drugs</b>	Desmopressin

Adapted from Porte RJ, Leebeek FWG. Pharmacological strategies to decrease transfusion requirements in patients undergoing surgery. *Drugs* 2002;62:2193–2211.

thopaedic patients undergoing hip or knee arthroplasty have shown a decreased requirement for perioperative blood transfusion when erythropoietin has been administered several weeks before surgery. Some studies have shown generation of substantial (up to 1102 mL) red blood cell production, when exogenous erythropoietin has been administered. Antifibrinolytic agents should be considered when there is an imbalance between coagulation and fibrinolysis. Other pharmacologic aids that help control perioperative blood loss include topical agents (e.g., thrombin) and procoagulant drugs such as desmopressin (Table 22.2).

There are numerous methods (some outlined previously) for minimizing intraoperative blood loss and decreasing perioperative allogeneic blood transfusion requirements. To date, none of these methods has been shown to decrease the duration of hospital stay. In view of the multiplicity of methods available, it is important for institutions to establish and implement transfusion guidelines with appropriate transfusion thresholds and individualized to each patient (Table 22.3). The techniques discussed in this case can be used alone or in combination and should be tailored to meet the needs of each patient.

**TABLE 22.3** Examples of Blood Transfusion Indications

Patient with acute blood loss >20% of blood volume: Transfuse	
Hemoglobin/hematocrit <10 g/dL or 30%, ask:	
<ul style="list-style-type: none"> <li>• History of coronary artery disease</li> <li>• History of stroke</li> <li>• History of valvular heart disease</li> <li>• Syncope</li> <li>• Tachycardia</li> <li>• Angina</li> <li>• Hypoxemia</li> <li>• Mental status changes</li> <li>• Electrocardiogram changes</li> <li>• Decreased mixed venous oxygenation</li> </ul>	<p style="text-align: center;">If yes to any → Consider transfusion</p>

## KEY MESSAGES

1. Blood transfusion risks can often be minimized if strategies are used to avoid allogeneic blood transfusion.
2. Perioperative blood conservation requires collaboration and planning by members of the surgical and anesthesia teams.
3. Multiple techniques may need to be combined to minimize perioperative blood loss and decrease the need for allogeneic blood transfusion. Examples of blood conservation techniques include acute normovolemic hemodilution, controlled hypotension, ABD, and cell salvage/reinfusion.
4. ABD as well as donor-directed blood donation can still pose some risks that are associated with banked blood from anonymous donors.

## QUESTIONS

1. When comparing ABD to ANH as blood conservation strategies, ABD:
  - A. Is more cost-effective than ANH
  - B. Is more efficacious than ANH
  - C. Produces better preservation of platelet function than ANH
  - D. Is less likely to be associated with clinical errors than ANH
  - E. Results in bacterial contamination of blood more often than ANH

Answer: E
2. The most efficacious of the following techniques to reduce perioperative blood transfusion is:
  - A. Acute normovolemic hemodilution
  - B. Autologous blood donation
  - C. Induced hypotension
  - D. Intraoperative antifibrinolytic drug use
  - E. Lowered transfusion thresholds

Answer: E
3. Which of the following patient conditions is most likely to contradict the use of autologous blood donation?
  - A. A history of congestive heart failure
  - B. Preoperative anemia
  - C. Insulin-dependent diabetes mellitus
  - D. Moderate aortic stenosis
  - E. A history of a prior stroke

Answer: B

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# Transfusion Thresholds and Intraoperative Coagulopathy

Anthony Hennessy

## CASE FORMAT: REFLECTION

A 69-year old, 70-kg man was admitted to hospital on the day before planned revision hip arthroplasty. He had undergone an ipsilateral total hip replacement 6 years previously. This hip had caused him severe pain and disability for the preceding 4 months. Four years previously, he had suffered "a small heart attack" for which he spent 5 days in a distant hospital. He had not experienced angina since then and described good exercise tolerance, playing a round of golf 3 days a week up to 4 months previously when his mobility had deteriorated. He was taking aspirin 75 mg a day, which he had discontinued 7 days previously as per his surgeon's request. The patient was also taking bisoprolol 10 mg daily and pravastatin 20 mg daily.

The patient's clinical examination was unremarkable: blood pressure, 135/81 mm Hg (mean arterial pressure, [MAP] 95 mm Hg); electrocardiogram (ECG) showed sinus bradycardia at 58 beats per minute (BPM) with no other abnormality; chest radiograph was normal; hemoglobin (Hb) level, 12.1 g/dL; and other laboratory results were within normal limits. The blood bank made four units of cross-matched packed red blood cells (PRBC) available on request.

A 20-gauge radial arterial cannula, a 14-gauge intravenous cannula, and a triple-lumen central venous catheter were inserted, and administration of Hartmann's solution (1 L) was started preoperatively. A combined spinal epidural was placed at L3 to L4 using an 18-gauge Tuohy needle and a 27-gauge pencil point spinal needle. Isobaric bupivacaine 0.5% (2 mL) was injected intrathecally followed by bupivacaine 0.5% (5 mL) epidurally producing a satisfactory sensory block to T10. Midazolam 2 mg was administered; oxygen (O<sub>2</sub>) at 28% via face mask was applied, a temperature-monitoring urinary catheter was inserted, and the patient was draped and prepared for surgery. Surgery commenced with O<sub>2</sub> saturations of 97%, heart rate 68 BPM, and the patient's MAP was 71 mm Hg.

The anesthetist calculated a maximal allowable blood loss (MABL) to a minimum Hb of 8 g/dL based on the patient's stable ischemic heart disease using the formula:

$$\text{MABL} = \left[ \frac{(\text{initial Hb} - \text{minimum allowable Hb})}{\text{initial Hb}} \right] \times (\text{weight in kg}) \times (\text{mL of blood per kg body weight}).$$

$$\left( \frac{12.1 - 8.0}{12.1} \right) \times 70 \times 72 = \text{MABL of 1708 mL}.$$

An extended incision was required, as surgical access was difficult. Despite careful surgical technique, the patient bled at a steady rate, losing 600 mL of blood during the first hour. Ephedrine 6 mg  $\times$  2 was administered to maintain MAP >70 mm Hg during that time. Removing the old prosthesis and cement with exposure of cancellous acetabular and femoral bone led to ongoing hemorrhage despite packing of the femur.

After 2 hours of surgery, the patient's estimated blood loss was 1300 mL. He had received 2 L of Hartmann's solution with 500 mL of colloid and five aliquots of ephedrine (each 6 mg) to maintain MAP >70 mm Hg and urine output >50 mL per hour. An epidural bolus of bupivacaine 0.5% 5 mL had been administered to maintain adequate sensory block. The patient's SpO<sub>2</sub> was 97%, his heart rate was 82 BPM, and ECG ST monitoring was unchanged. His core temperature was 35.9°C. Arterial blood gas analysis demonstrated the patient's Hb level was 9.1 g/dL, and his serum lactate level was 3.1 mmol/L. Having decided that a transfusion threshold of 8.0 g/dL was reasonable, the anesthetist requested two units of PRBCs and decided to recheck the Hb in 1 hour. Surgeons described the patient as "oozy" and murmured about the aspirin effect. A coagulation screen was dispatched to the laboratory.

The patient required aliquots of ephedrine with greater frequency over the following 30 minutes to maintain MAP >70 mm Hg, and the anesthetist decided to transfuse the two units of PRBC, as there was ongoing hemorrhage.

After reconstruction of the acetabular cup using bone graft, wires, and an acetabular cage, reaming commenced on the femur with a visible increase in blood loss.

The patient's MAP decreased to 55 mm Hg, his heart rate increased to 88 BPM, and his core temperature decreased to 35.3°C. The anesthetist administered 100  $\mu$ g aliquots of phenylephrine to maintain the patient's MAP >60 mm Hg.

Repeat analysis showed that the patient's Hb concentration was 7.7 g/dL, and his serum lactate levels were 5.8 mmol/L. The anesthetist requested and transfused two further units of PRBC and ordered four more (he was informed that those would be available in 1 hour). The results of the coagulation screen were telephoned to the operating room: the international normalized ratio was 1.7, and the activated partial thromboplastin time was 41 seconds.

Two units of fresh frozen plasma were transfused. The femoral shaft required bone graft before insertion of the femoral prosthesis, which was eventually accomplished after

3 hours. The surgery continued with measurement and fitting of the femoral component requiring one change followed by closure. The total blood loss was estimated to be 2110 mL.

The patient was transferred to the postanesthetic care unit. His vital signs were stable as follows: MAP, 61 mm Hg; SpO<sub>2</sub>, 97%; heart rate, 91 BPM; and a temperature of 35.1°C. He complained of feeling cold and was shivering. One hour postoperatively, Hb concentration was 8.7 g/dL, international normalized ratio was 1.9, and activated partial thromboplastin time was 44 seconds. There was ongoing loss in the drains. One unit of PRBC was transfused, and two additional units of fresh frozen plasma and one unit of cryoprecipitate were administered.

The patient developed chest pain with ST depression on ECG during the night and required transfer to the coronary care unit. He remained there for 3 days during which T-wave inversion on ECG and an increase in serum troponin levels were diagnostic of a subendocardial myocardial infarct.

## CASE DISCUSSION

Revision hip arthroplasty is performed commonly, as primary hip arthroplasty is associated with a 10% failure rate by 10 years. Reasons for failure include aseptic loosening, instability, and infection. Removing the implanted prosthesis and exposing cancellous bone of both the acetabulum and femur leads to prolonged exposure of, and bleeding from the medullary vasculature. The associated blood loss is substantial, as the mean intraoperative blood loss was 2249 mL (range, 900–5600 mL) by one estimate.<sup>1</sup>

The World Health Organization defines anemia as a Hb level <13 g/dL.<sup>2</sup> In general, for patients undergoing noncardiac surgery, preoperative anemia is associated with a poor postoperative outcome. A large recent retrospective study showed a 1.6% increase in 30-day postoperative mortality for each percentage-point increase or decrease in the hematocrit value from normal.<sup>3</sup> Mild degrees of anemia have been associated with worse outcomes in patients with ischemic heart disease.<sup>4</sup> Early preoperative screening for elective surgery and intervention to investigate anemia and optimize Hb levels would reduce transfusion and improve outcome. Thirty days before surgery is an appropriate time for screening to allow for optimization.<sup>5</sup> A combination of appropriate investigations and therapy using iron, folate, vitamin B<sub>12</sub>, and erythropoietin can be used. Commonly used erythropoietin regimens include<sup>6</sup> 600 units/kg weekly × four doses 300 units/kg for 15 days.

Preoperative autologous blood donation is useful in decreasing allogenic transfusion exposure but requires rigorous organization and planning to be of value.<sup>7</sup> There is a risk of adverse reactions to and infections from blood storage. It is probably not the optimal management for a patient with ischemic heart disease such as in the case discussed. This type of treatment would not outweigh the benefits of Hb optimization with erythropoietin.

## Antifibrinolytic Therapy

Aprotinin has been used with success in decreasing blood loss in orthopaedic surgery including spine, hip, and knee surgery. Aprotinin decreases the systemic inflammatory response, fib-

rinolysis, and thrombin generation, resulting in less allogeneic blood transfusion and less bleeding. For revision or bilateral hip arthroplasty, blood loss is decreased through the administration of aprotinin by 25% to 50% in various studies.<sup>8</sup> There are concerns about adverse thrombogenic and renal effects of aprotinin.<sup>9</sup> A recent prospective randomized controlled trial in patients undergoing high-risk cardiac surgery has shown an excess mortality rate in patients who received aprotinin compared with those who received tranexamic acid or aminocaproic acid.<sup>10</sup> The excess mortality occurred despite a greater decrease in blood loss in the aprotinin group.

Tranexamic acid inhibits fibrinolysis by blocking the lysine binding sites of plasminogen to fibrin. Studies have shown a reduction in blood loss of 43% to 54% in patients undergoing knee surgery.<sup>11</sup> Conclusive evaluation of potential prothrombotic adverse effects and demonstration of beneficial effects on reducing blood loss in orthopaedic surgery are required before the routine use of tranexamic acid can be recommended for hip revision arthroplasty.

## Intraoperative Blood Salvage

Perioperative red cell salvage and filtration, combined with appropriate washing of red blood cells and retransfusion is an appropriate therapy to decrease allogenic transfusion provided that infection and malignancy have been excluded. The available evidence supports its use when the expected blood loss is >1500 mL. Adverse effects include transmission of infection and possibly worsening of coagulopathy.<sup>12</sup> Use of a blood salvage system in the case discussed would have decreased the patient's exposure to allogenic transfusion and the risks of associated adverse effects.

## Transfusion Thresholds/Maximal Allowable Blood Loss with Coexisting Ischemic Heart Disease

Calculating a maximal allowable blood loss for an individual patient is useful and is usually based on a formula first popularized by Gross.<sup>13</sup> Selecting the initial Hb as the denominator results in a conservative estimate of MABL. Variations using mathematical modeling with different hemoglobin or hematocrit values and incorporating ongoing hemodilution and cell salvage have been reported.<sup>14</sup>

The Transfusion Requirement in Critical Care trial has produced excellent prospective data on transfusion requirements in chronic stable critical care patients.<sup>15</sup> The trial excluded patients with active hemorrhage and other acute hemodynamic insults. The outcome was no worse in the group for whom a transfusion threshold was 7.0 g/dL as compared with that for whom the threshold was 9.0 g/dL. The only patient subgroup with evidence of poorer outcome in the lower threshold arm was patients with known ischemic heart disease.

These data cannot be extrapolated to calculate MABL in the hemorrhaging patient. Similarly, the use of these hemoglobin values to rigidly define transfusion thresholds intraoperatively would not be appropriate. O<sub>2</sub> consumption and utilization are markedly different in patients with intraoperative hemodynamic stress and hemorrhage compared with recovering stable critical care patients.

The poorer outcome of patients with unstable ischemic heart disease in the lower threshold group in the Transfusion Requirement in Critical Care trial may be relevant to the

management of the patient described in this case. It is difficult to define the point at which O<sub>2</sub> consumption/extraction by myocardial tissue is maximal and can only be improved by augmenting the O<sub>2</sub> carrying capacity.

The best evidence currently available supports the following:

- Hb >10 g/dL: Transfusion is unlikely to be useful.
- Hb <7 g/dL: Transfusion is likely to be useful.

Between these levels, the decision to transfuse should be based on the rate of blood loss and ongoing loss supported by laboratory and clinical evidence of inadequate tissue oxygenation.

Maximal allowable blood loss and Hb thresholds are very useful for guidance at the outset but are difficult to apply satisfactorily in patients with ongoing substantial hemorrhage. The rate of early blood loss, the identified risk of perioperative acute coronary syndrome, and the known complexity and duration of this surgery should have prompted an earlier intervention to optimize O<sub>2</sub> carrying capacity.

### Intraoperative Hypothermia

Mild perioperative hypothermia (<1°C) increases blood loss by approximately 16% (4%–26%) and increases the relative risk for transfusion by approximately 22% (3%–37%).<sup>16</sup> Maintaining perioperative normothermia decreases blood loss and transfusion requirement by clinically important amounts.<sup>16</sup> Shivering will increase O<sub>2</sub> consumption contributing further to tissue hypoxia and critical organ ischemia. Aggressive intraoperative warming reduces blood loss during hip arthroplasty.<sup>17</sup> Perioperative hypothermia also adversely affects wound healing.<sup>18</sup> In the case discussed, development of intraoperative hypothermia was the most preventable factor that contributed to the adverse patient outcome.

### Perioperative Coagulopathy

Coagulopathy can develop in patients with substantial hemorrhage as a result of hemodilution, hypothermia, administration of fractionated blood products, and disseminated intravascular coagulation.

The decision when and if to discontinue antiplatelet medication or other anticoagulants is important and difficult. This case highlights these difficulties, as discontinuing antiplatelet medication increases the risk of postoperative myocardial infarction by a factor of three, and continuation will increase hemorrhage volume by a factor of 1.5. In the elective setting, multidisciplinary assessment of the risk/benefit ratio for each individual patient will be necessary to optimize outcome and minimize risk in the perioperative period.<sup>19</sup>

Intraoperative and postoperative management of potential or actual coagulopathy includes (a) visual assessment of the surgical field for microvascular bleeding and laboratory monitoring for coagulopathy, (b) transfusion of platelets, (c) transfusion of fresh frozen plasma, (d) transfusion of cryoprecipitate, (e) administration of drugs to treat excessive bleeding (e.g., desmopressin, topical hemostatics), and (f) recombinant activated factor VII.

The American Society of Anesthesiologists guidelines state that, in a patient with ongoing bleeding:

1. Platelets should be administered when the count is <50,000 cells/mm<sup>3</sup>.

2. Fresh frozen plasma should be administered when the international normalized ratio or activated partial thromboplastin time is elevated.
3. Cryoprecipitate should be administered when fibrinogen concentrations are <80 mg/dL (2.3 umol/L).

These guidelines also indicate that recombinant activated factor VII is an appropriate rescue drug when traditional, well-tested options have been exhausted.<sup>20</sup>

Development of coagulopathy in the case described herein was multifactorial. Observation of the surgical field and communication with the surgical team would have led to earlier awareness of the need for intervention.

### KEY MESSAGES

1. Anemia requires investigation and treatment before major elective surgery.
2. Estimates of transfusion thresholds, maximum allowable blood loss, and rates of ongoing blood loss should be used to guide transfusion.
3. Intraoperative red cell salvage can reduce allogenic transfusion.
4. Preoperative consideration should be given to aggressive maintenance of intraoperative normothermia.
5. In the operative setting, abnormal excessive bleeding or "ooze" can provide early evidence of coagulopathy.

### QUESTIONS

1. What is the result of choosing "initial Hg" as the denominator when calculating MABL?  
Answer: A conservative (small) estimate of MABL results.
2. At what level of anticipated blood loss in intraoperative cell salvage viable?  
Answer: 1500 mL
3. What is the effect of mild intraoperative hypothermia (<1°C) on blood loss?  
Answer: It substantially increases intraoperative blood loss (approximately 16%).

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# Anesthesia for Bariatric Surgery

Christopher J. O'Connor

## CASE FORMAT: REFLECTION

A 44-year-old, 5' 11", 170-kg man (body mass index [BMI], 52) with a history of hypertension, obstructive sleep apnea (OSA), and non-insulin-dependent diabetes mellitus presented for laparoscopic gastric bypass surgery. His medications included metoprolol, pioglitazone, and hydrochlorothiazide. He had a continuous positive airway pressure (CPAP) machine at home but rarely used it. His preoperative assessment was remarkable for a serum glucose level of 200 mg/dL, an electrocardiogram showing left ventricular hypertrophy and right heart strain, and an echocardiogram revealing moderate tricuspid regurgitation, right ventricular hypertrophy, and estimated peak systolic pulmonary artery pressure of 45 mm Hg. The patient's left ventricular function was normal. Physical examination revealed a morbidly obese man with clear lungs, normal heart tones, and a Mallampati grade III airway with a "thick neck" and limited cervical extension. It was noted that venous access would be difficult to secure. Baseline room air arterial oxygen saturation was 94%.

The patient was scheduled to undergo a laparoscopic gastric bypass procedure. A 22 gauge intravenous line was placed with difficulty, and famotidine 20 mg and metoclopramide 20 mg were administered intravenously, with 30 mL of sodium citrate. Midazolam 2 mg was administered intravenously before insertion of a radial arterial catheter. In the operating room, standard monitoring was commenced, and topical anesthesia was applied to the patient's oropharynx. A transtracheal injection of 4% lidocaine was performed, as was an awake fiberoptic intubation. A pulmonary artery catheter was inserted via the right internal jugular vein using ultrasound guidance. After anesthesia induction, intermittent positive pressure was instituted using a tidal volume of 8 mL/kg, respiratory rate of 14 breaths per minutes, 60% inspired oxygen, and 7 cm H<sub>2</sub>O positive end-expiratory pressure. Peak airway pressures of 36 cm H<sub>2</sub>O were observed. The patient's anesthetic consisted of a neuromuscular blockade with vecuronium, a remifentanyl infusion at 0.5 mcg/kg per minute, and 1% to 1.5% inspired sevoflurane. The procedure was completed in 3 hours, with blood loss of 250 mL, and 4.2 liters of Lactated Ringer's solution was used as a fluid replacement. An insulin infusion was used to maintain normoglycemia. At the end of surgery, 60 mg of ketorolac and 4 mg of ondansetron were administered. The patient's trachea was successfully extubated, and he was transferred to the surgical intensive care

unit with a non-rebreather oxygen face mask in place. He remained in the surgical intensive care unit for 24 hours for cardiopulmonary monitoring, glycemic control, and to facilitate the use of CPAP. The patient was discharged home after 5 days but returned after 2 weeks with a suspected pulmonary embolus. This was treated with intravenous heparin and subsequently with subcutaneous low-molecular-weight heparin before being discharged home for the second time.

## CASE DISCUSSION

Bariatric surgery has been shown to be more efficacious than any other method of weight reduction, and several studies have shown consistent reductions in weight and the incidence of related comorbidities, as well as overall mortality.<sup>1,9,11,13</sup> There is a significant reduction in the incidence of hyperlipidemia, hypertension, type 2 diabetes, and OSA accompanying the weight loss induced by bariatric surgery.<sup>3</sup> Classification of obesity is shown in Table 24.1.

Bariatric surgery encompasses several types of procedures, broadly classified as either restrictive (gastric banding, vertical-banded gastroplasty, malabsorptive [biliopancreatic diversion]), or combined procedures (gastric bypass) (Fig. 24.1). Restrictive procedures cause weight loss by limiting the stomach's capacity to accommodate food, whereas malabsorptive surgery involves bypass or resection of the stomach and bypass of long segments of the small intestine to reduce the area for nutrient absorption. Gastric bypass is a combined procedure that involves dividing the stomach into a small, proximal pouch and a separate, large, distal nonfunctional remnant. The upper pouch is then attached to the jejunum through a small gastrojejunal anastomosis. The proximally divided jejunum is then reattached to the jejunum 75 to 150 cm below the gastrojejunal anastomosis, thus creating a Roux-en-Y limb.<sup>5</sup> Malabsorptive surgery is effective but causes more severe postoperative metabolic complications, whereas purely restrictive procedures produce less durable weight loss than gastric bypass. Laparoscopic gastric bypass appears to be the most efficacious of all bariatric procedures.

## Airway Management

Morbid obesity and OSA, a common comorbid condition, can make mask ventilation difficult. Proper positioning of the obese patient with blankets to elevate the head and shoulders ("ramped" position) has been shown to improve laryngeal exposure. Although some evidence suggests more difficult

**TABLE 24.1** Classification of Obesity

Classification	Body Mass Index
Overweight	25 kg/m <sup>2</sup>
Obese	30 kg/m <sup>2</sup>
Morbidly obese	40 kg/m <sup>2</sup>
Super obese	50 kg/m <sup>2</sup>

intubation in morbidly obese patients, a study of 100 morbidly obese patients found that neither obesity nor BMI predicted difficult intubation, but rather large neck circumference (a marker of OSA) and a greater Mallampati score were predictive. Obese patients, however, desaturate O<sub>2</sub> more quickly than nonobese individuals after the induction of apnea and general anesthesia; as a result, thorough preoxygenation is essential. Moreover, if there is any question about the potential difficulty of tracheal intubation, an awake intubation technique should be strongly considered.

Just as the approach to tracheal intubation should be approached with caution, the timing and decision regarding extubation should also be managed conservatively. Many clinicians choose postoperative mechanical ventilation in the super obese or for patients undergoing open, rather than laparoscopic, procedures.

### Anesthetic Management

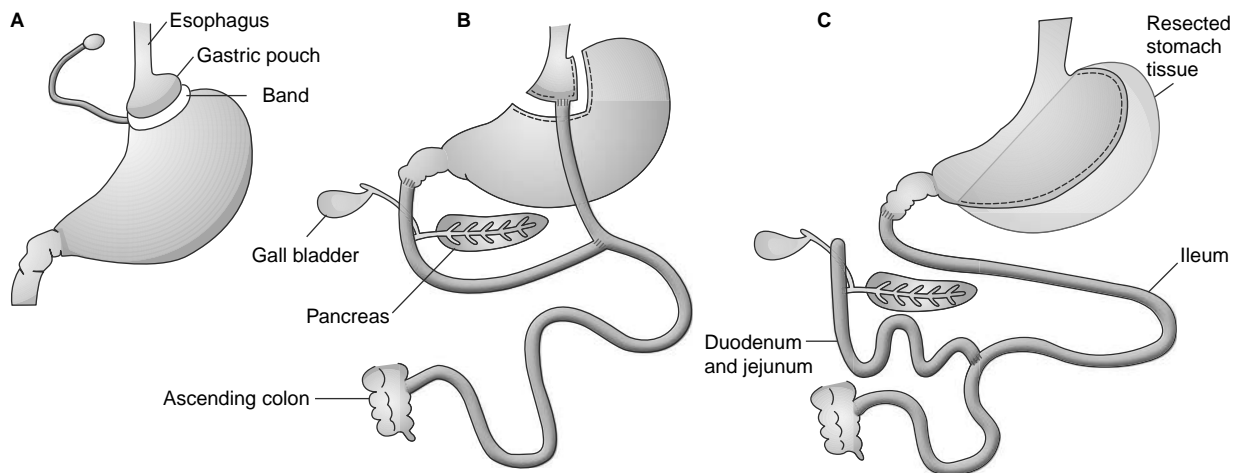
Drug pharmacokinetics differ in morbidly obese patients. Propofol dosing can be determined using total body weight, rather than ideal or lean body weight.<sup>16</sup> Because of their lipophilicity, thiopental and benzodiazepines may need to be administered in greater doses to obese than to nonobese patients. Opioid pharmacokinetics are more complex, with limited data

suggesting that remifentanyl and fentanyl dosing should be based on ideal body weight, whereas sufentanyl dosing can be accurately predicted using total body weight. Neuromuscular blocking drug dosing is more predictable because of the hydrophilic nature of nondepolarizing agents. Both vecuronium and rocuronium should be dosed based on ideal body weight to avoid prolonged neuromuscular blockade. Although all volatile agents can be safely used in morbidly obese patients, desflurane and sevoflurane are associated with more rapid emergence than isoflurane. Dexmedetomidine—a selective  $\alpha_2$ -adrenergic agonist—may reduce intraoperative opioid requirements, while also improving intraoperative hemodynamics.<sup>2,4</sup> Epidural analgesia, although technically more difficult to administer in the morbidly obese, improves postoperative analgesia, as does the use of incisional local anesthetic infiltration.<sup>12</sup>

Ultimately, no one anesthetic technique has been shown to be superior to another for morbidly obese patients undergoing bariatric surgery, but the presence of OSA and common sense suggest that anesthetic techniques that employ shorter-acting agents may allow a more prompt recovery, less postoperative respiratory depression, and a more rapid return to baseline respiratory function.

### Intraoperative Monitoring

There is little evidence that morbidly obese patients require more intense cardiovascular monitoring during bariatric surgery than nonobese patients.<sup>6</sup> The presence of significant comorbidities should guide the use of more invasive monitors. Patients with pulmonary hypertension, however, such as those with OSA or super obesity, may require the use of a pulmonary artery catheter. Difficulties with peripheral venous access and blood sampling are facilitated by inserting a central venous catheter, often using ultrasound guidance. Finally, it may be necessary to place intra-arterial catheters because of technical difficulties associated with blood pressure cuffs.



**Figure 24.1** • (A) Adjustable gastric banding. An inflatable silicone band around the upper stomach partitions it into a ~30-mL proximal pouch and a large, distal remnant, connected through a narrow, nondistensible adjustable constriction. (B) Gastric bypass divides the stomach into a small, proximal pouch measuring ~30 mL and a separate, large, distal defunctionalized remnant. The upper pouch is joined to the jejunum through a narrow distensible gastrojejunal anastomosis. The proximally divided jejunum is reattached to the jejunum 75 to 150 cm below the gastrojejunal anastomosis creating a Roux-en-Y limb. (C) Biliopancreatic diversion, with or without a pylorus-sparing “duodenal switch” causes malabsorption as pancreatic and biliary secretions are diverted to the distal small intestine approximately 50 cm from the ileocecal valve. Absorption is thus limited to the distal ileum. A “sleeve” gastrectomy is depicted. (From Kral JG, Näslund E. Surgical treatment of obesity. *Nature Clinical Practice Endocrinology & Metabolism* 2007;3:574–583.)

**TABLE 24.2** Risk Factors for Postoperative Complications

- Age >45
- Male gender
- Super obesity (body mass index >50 kg/m<sup>2</sup>)
- Pulmonary hypertension
- Obstructive sleep apnea

### Patient Outcome

The overall rates of mortality and morbidity associated with bariatric surgery are less than 1% and 15%, respectively, although rates may be greater for open versus laparoscopic procedures and for patients with multiple comorbidities. A variety of risk factors have been identified by multivariate analyses and risk models as predictive of mortality. These include male gender, age >45 years, BMI >50 kg/m<sup>2</sup>, and the presence of OSA/pulmonary hypertension (Table 24.2).<sup>7,8</sup> Postoperative mortality appears to be secondary to pulmonary embolism/deep venous thrombosis, intra-abdominal leaks/sepsis, and myocardial infarction. Other nonfatal complications include wound infection, pneumonia, ventral hernias, nutritional deficiencies, and surgical events related to a given procedure (e.g., pouch enlargement, band slippage).

### CONCLUSION

For morbidly obese patients, bariatric surgery is an effective method of weight reduction that decreases the incidence of comorbidities as well as long-term mortality.

### KEY MESSAGES

1. Morbidly obese patients have a high incidence of comorbidities, including diabetes mellitus, hypertension, OSA, gastroesophageal reflux disease, and pulmonary hypertension/right heart dysfunction.
2. Important anesthetic considerations include selective use of special monitors (often intra-arterial and central venous catheters), conservative airway management, insulin therapy to maintain normoglycemia, and the use of short-acting anesthetic agents.
3. Intraoperative ventilatory management should employ high-inspired oxygen concentrations and 5 to 10 cm H<sub>2</sub>O-positive end-expiratory pressure. Postoperative care should include aggressive cardiopulmonary monitoring for select patients with significant comorbidities and the use of CPAP for patients with OSA.
4. Perioperative management and postoperative morbidity and mortality are related to several risk factors, as well as the preoperative BMI, and super-obese patients (BMI >60) have the greatest incidence of complications.

### QUESTIONS

1. The incidence of which of the following conditions is least reduced by bariatric surgery?
  - A. Hypertension
  - B. Coronary artery disease
  - C. Diabetes mellitus
  - D. Hyperlipidemia
  - E. Sleep apnea

Answer: B

2. Which of the following medications should dosing be based on total body weight?
  - A. Fentanyl
  - B. Rocuronium
  - C. Propofol
  - D. Remifentanyl
  - E. Vecuronium

Answer: C

3. Which of the following patient characteristics increases morbidity and mortality after bariatric surgery?
  - A. > Female gender
  - B. BMI >40 kg/m<sup>2</sup>
  - C. Age >40 years
  - D. OSA
  - E. Presence of diabetes mellitus

Answer: D

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# Vasopressin and Resuscitation

Stephen F. Dierdorf

## CASE FORMAT: REFLECTION

A 75-year-old, 95-kg male patient with a 4-day history of worsening abdominal pain presented for an emergency laparotomy for a suspected perforated duodenal ulcer. His coexisting medical conditions included hypertension treated with daily losartan 100 mg and coronary artery disease. He underwent coronary artery bypass grafting at age 72 and has been free of cardiac symptoms since.

The preoperative assessment performed in the emergency department showed a patient in obvious discomfort with a blood pressure of 100/60 mm Hg, heart rate of 110 beats per minute, and a respiratory rate of 28 breaths per minute. His temperature was 39°C. The patient was receiving supplemental oxygen via nasal cannula at 4 liters per minute, and arterial saturation by pulse oximetry was 96%. There had been no urine output since arrival at the hospital. Laboratory results obtained upon admission to the emergency department were as follows: hemoglobin, 15 g/dL; hematocrit level, 45%; serum potassium, 4.3 mEq/L; sodium, 140 mEq/L; bicarbonate, 18; blood urea nitrogen, 35; and creatinine, 1.0. The echocardiogram readings showed first-degree atrioventricular block with normal QRS morphology. The patient was taken to the operating room for exploratory laparotomy, and standard monitors were applied. After preoxygenation and pretreatment with 2 mg cis-atracurium, anesthesia was induced with propofol 100 mg. Succinylcholine 160 mg was administered to facilitate tracheal intubation, which was performed without difficulty with an 8-mm inner diameter tracheal tube. Soon after induction, the patient's blood pressure decreased to 60/20 mm Hg, and his heart rate increased to 140 beats per minute (BPM). ST depression appeared in the inferior leads on the surface echocardiogram. Immediate treatment consisted of the intravenous infusion of norepinephrine at 5 µg per minute, increasing to 30 µg per minute, the administration of 1500 mL of Lactated Ringer's solution, and 500 mL of 5% albumin. Despite this treatment, the patient's blood pressure continued to decline, his blood pressure became unmeasurable, and his heart rate decreased to 55 beats per minute. Epinephrine 1 mg was administered intravenously. The patient's heart rate increased to 120 BPM, and his blood pressure increased to 30/15 mm Hg. A second dose of epinephrine 1 mg increased his heart rate to 160 BPM and produced frequent premature ventricular contractions leading to ventricular tachycardia and ventricular fibrillation.

DC countershock was unsuccessful and asystole developed. Forty units of intravenously administered vasopressin resulted in spontaneous cardiac activity and an increase in blood pressure to 60/30 mm Hg. During the next 5 minutes, 500 mL of 5% albumin was administered, and a continuous vasopressin infusion at 0.2 units per minute was initiated. The patient's heart rate and blood pressure stabilized at 90 BPM and 100/50 mm Hg, respectively.

## CASE DISCUSSION

This case is representative of the course of anesthesia for an elderly patient with significant preoperative physiologic derangement. The cause of clinically significant hypotension during anesthesia is not always clear, and there are many treatment options. Ideally, a definitive cause for the hypotension can be elucidated, and specific therapy can then be instituted. The goal of resuscitation is restoring vital organ perfusion and function. In some cases, the presumptive diagnosis is accurate, but therapy is controversial. The controversy surrounding resuscitation concerns the role of vasopressors and volume expansion: Is one better than the other, or is combination therapy better? Clinical studies of cardiac arrest are difficult because of the large number of variables and the lack of a matched control group. Animal models of cardiac arrest and shock have been developed, but the ability to translate those findings to real-world patients is unknown. The vasopressors most frequently used for resuscitation from cardiac arrest have been epinephrine and norepinephrine. Although the vasoconstrictive effects of vasopressin have been known for more than 100 years, it was not until the mid-1990s that vasopressin garnered much scientific attention for resuscitation.

Vasopressin, an antidiuretic hormone, is a naturally occurring nonapeptide synthesized in the hypothalamus and stored and secreted by the posterior pituitary. Vasopressin release is triggered by increased plasma osmolarity, decreased blood pressure, and decreased cardiac filling (hypovolemia). Three vasopressin receptors have been identified: V<sub>1</sub> mediates vasoconstriction, V<sub>2</sub> acts on the renal collecting tubules and causes water retention, and V<sub>3</sub> mediates corticotrophin release in the central nervous system. Stimulation of V<sub>1</sub> receptors on vascular smooth muscle cells mobilizes intracellular calcium and increases extracellular calcium influx, thereby causing vasoconstriction (Table 25.1).<sup>1,2</sup> The metabolic effects of vasopressin are mediated via V<sub>2</sub> and V<sub>3</sub> receptors and can influence a large number of physiologic systems.

**TABLE 25.1** Vasopressin Receptors and Effects

Receptor	Effector Site	Effect
V <sub>1</sub>	Vascular smooth muscle	Vasoconstriction
	Platelets	Aggregation
	Brain	Baroreflex mediation
V <sub>2</sub>	Renal collecting duct cells	Antidiuresis
V <sub>3</sub>	Anterior pituitary	ACTH secretion

ACTH, adrenocorticotrophic hormone.

The metabolic effects of vasopressin in critically ill humans, however, have not been extensively studied. Current knowledge suggests that vasopressin does not alter glucose, lactate, or electrolyte levels; may reduce oxygen demand; and preserves pulmonary arterial endothelial function.<sup>3</sup> The plasma half-life of vasopressin is 4 to 20 minutes. Terlipressin is a synthetic analog of vasopressin with a half-life of 6 hours. Vasopressin contributes little to blood pressure control during normal physiologic conditions. When other compensatory mechanisms are not effective, vasopressin becomes an important mechanism for normalizing hemodynamics. Metabolic acidosis attenuates the effects of catecholamines. The vasoactive effects of vasopressin, however, are unaffected by acidosis. Vasopressin may be more effective than catecholamines if acidosis is present or when catecholamines become ineffective. Low-dose vasopressin may produce vasodilation in the coronary and cerebral arterial beds and increase myocardial blood flow (Table 25.2).<sup>4</sup>

There are five different scenarios for which vasopressin may be efficacious: (a) cardiac arrest, (b) vasodilatory shock, (c) anaphylactic shock, (d) hemorrhagic shock, and (e) during liver transplantation.

**Cardiac Arrest** Despite early reports of success in a small number of patients suffering cardiac arrest in 1996, subsequent human and animal research has not fully clarified the role of vasopressin for resuscitation.<sup>5–9</sup> Epinephrine has been the mainstay of pharmacologic therapy for cardiac arrest for decades. Vasopressin may offer some advantages in patients

with asystole, and a combination of epinephrine (1 mg) and vasopressin (40 units) may be better than either drug alone. Current recommendations are that vasopressin (40 units) may be substituted for the first or second dose of epinephrine (1 mg) during cardiac arrest. The outcome from out-of-hospital cardiac arrest is very poor, and survival rates worldwide average 6%. Survival rates from out-of-hospital witnessed ventricular fibrillation have, however, been reported to be as high as 74%. This success is predicated on laypersons trained in cardiopulmonary resuscitation and the immediate availability of defibrillators. Patients in the operating room are well monitored, and adverse events can be detected early and managed with highly controlled interventions.

**Septic Shock** The cornerstones of therapy for vasodilatory or septic shock have been antibiotics, volume resuscitation, and catecholamines. The key to improved survival in patients with septic shock is rapid intervention. Current recommendations for the treatment of septic shock include administration of antibiotics and volume resuscitation to maintain a central venous pressure of 8 to 12 mm Hg and a mean arterial blood pressure of 65 mm Hg or greater. If volume administration does not produce the desired hemodynamic responses, norepinephrine and dopamine are the vasoactive drugs of choice.<sup>10</sup> In cases of septic shock refractory to catecholamines or at doses that cause side effects such as tachydysrhythmia, vasopressin increases blood pressure and permits a reduction in catecholamine doses. Vasopressin in high doses can cause mesenteric vasoconstriction to the point of intestinal ischemia. In low doses, vasopressin appears to improve gastrointestinal perfusion. A continuous vasopressin infusion may be preferable to intermittent bolus doses of the longer-acting terlipressin to reduce the likelihood of mesenteric vasoconstriction and gastrointestinal ischemia.

**Anaphylactic Shock** Recommended therapy for anaphylactic shock is fluid administration and epinephrine. Vasopressin has been shown to completely reverse histamine-induced vasodilation, whereas epinephrine results in only partial reversal. Until further definitive evidence exists, vasopressin is a reasonable choice when epinephrine fails to produce hemodynamic stability.<sup>11</sup>

**Hemorrhagic Shock** The goals of resuscitation from hemorrhagic shock have been to restore circulating blood volume to preserve or improve vital organ perfusion and function. There is increasing evidence in animal models that volume resuscitation alone produces a worse outcome than limited volume resuscitation in combination with vasopressin or norepinephrine.<sup>12</sup> The precise mechanism of improved outcome with vasopressin remains to be elucidated. Proposed mechanisms include vasopressin-induced vasoconstriction shifting blood from the wound site and an increase in circulating vasopressin levels from depleted endogenous stores. Successful resuscitation with vasopressin may be dose dependent. Low-dose vasopressin may improve hemodynamics while avoiding the deleterious effects of organ ischemia from high doses of vasopressin.

**Liver Transplantation** Patients with liver failure have multi-system disease, and the development of hepatorenal syndrome

**TABLE 25.2** Vasopressin Doses

	Condition	Dose
Vasopressin	Cardiac arrest	0.5 units/kg (bolus)
	Hypotension	0.0002–0.002 units/kg per minute
Terlipressin	Hypotension	1 mg intravenously (repeat every 4–6 hours)

is a poor prognostic indicator. Low-dose vasopressin infusions may increase renal blood flow and have been used with some success in treating hypotension immediately after liver transplant. At present, research data are insufficient to determine the role of vasopressin in patients with liver failure.

**Intraoperative Hypotension** Patients receiving long-term therapy with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are more likely to develop hypotension during anesthesia. This hypotension may be resistant to treatment with catecholamines and volume expansion. The vasoconstrictive effect of vasopressin is independent of catecholamine and angiotensin receptors. Vasopressin has been shown to be effective for the treatment of hypotension in patients receiving those drugs.<sup>13</sup>

The use of vasopressin for patients with severe hypotension and shock is controversial. In milieu of the shock state, vascular smooth muscle may be less sensitive to, and even refractory to the effects of catecholamine. For patients who respond poorly to catecholamines, vasopressin provides another therapeutic option. Continued research should better define the role of vasopressin.

## SUMMARY

Hypovolemia and sepsis contributed to the intraoperative shock that occurred with the patient described in this case. Volume resuscitation does not always correct the hemodynamic instability caused by septic or hemorrhagic shock. Excessive fluid administration may, in fact, worsen the outcome. It is not always possible to know the patient's balance between endogenous substances and intravascular volume that results in hemodynamic stability. Choices to be made in this situation include how much and what type of fluid to administer and which, if any, vasoactive drugs should be given. Norepinephrine and epinephrine have been used for decades to treat hypotension and shock. Patients unresponsive to these drugs may develop side effects that offset the benefits as the dosages are increased. Vasopressin is a naturally occurring vasoactive substance that may be deficient in some patients and may require replacement therapy. Vasopressin in combination with catecholamines may improve the hemodynamic profile and permit a dose reduction of the catecholamines. The initial enthusiasm regarding vasopressin for resuscitation has been tempered by subsequent research. Vasopressin has a different mechanism of action at the cellular level than catecholamines, and the two different drugs may be complementary. If epinephrine administration fails to achieve the desired effect, vasopressin is the next best choice. Although the advantages of vasopressin as compared with other vasopressors for the treatment of shock are not yet clear, the timing of intervention may be critical.<sup>14,15</sup> The anesthesiologist can potentially intervene with effective treatment at the very early stages of shock, thus increasing the likelihood of a successful outcome. More selective uses of vasopressin in the operating room include treatment for anaphylactic shock, vasodilatory shock after cardiopulmonary bypass, and refractory hypotension in patients receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

## KEY MESSAGES

1. There are multiple causes of intraoperative hypotension and shock.
2. Vasopressin is effective for managing intraoperative hypotension caused by several factors.
3. Vasopressin complements epinephrine for resuscitation following cardiac arrest.
4. Successful resuscitation depends on early multimodal treatment.

## QUESTIONS

1. By what mechanism does vasopressin cause vasoconstriction?

Answer: Vasopressin stimulates vasopressin-1 receptors. Activation of these receptors increases calcium movement into vascular smooth muscle and results in vasoconstriction.

2. How does the effect of vasopressin differ from the effect of epinephrine when used for the treatment of cardiac arrest?

Answer: Vasopressin is effective in an acidotic milieu; whereas, the effect of epinephrine is attenuated by acidosis. Vasopressin does not cause tachycardia.

3. Does treatment with vasopressin produce a better outcome from cardiac arrest than treatment with epinephrine?

Answer: Despite initial reports of the efficacy of vasopressin for treatment of cardiac arrest, other studies have not confirmed the superiority of vasopressin. Nonetheless, vasopressin may be effective when epinephrine fails.

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# Anesthesia and Hypertension

Stephen F. Dierdorf

## CASE FORMAT: STEP BY STEP

A 56-year-old, 5'6", 127-kg male presented for resection of a right upper lung lobe mass via a right thoracotomy. The patient had a 3-month history of a dry cough. A chest radiograph and subsequent chest computed tomography scan revealed a 4-cm mass in the upper lobe of the right lung. Past surgical history included a right inguinal hernia repair at 18 years and a laparoscopic cholecystectomy at 46 years. The patient was diagnosed with hypertension at 47 years of age, and treatment at the time of surgery included an angiotensin receptor blocker (losartan) and an angiotensin-converting enzyme (ACE) inhibitor (lisinopril). During the past 4 years, his blood pressure had been labile and difficult to control. At times, a  $\beta$ -adrenergic blocker (metoprolol) was added to the treatment regimen. He had not taken metoprolol during the 3 months prior to surgery. The patient had a 5-year history of sleep apnea and used a continuous positive airway pressure machine at night. Physical examination revealed an obese male with no evidence of respiratory distress. The patient's blood pressure was 165/105 mm Hg, and his heart rate was 82 beats per minute. His laboratory testing values were as follows: hemoglobin level, 14.5; hematocrit, 43; sodium, 141 mEq/L; potassium, 4.3 mEq/L; fasting glucose, 83 mg/dL; creatinine, 1.0 mg/dL; and blood urea nitrogen, 10. The preoperative room air arterial blood gas was PaO<sub>2</sub>, 82; PaCO<sub>2</sub> 41; pH, 7.39, and base excess, 0. The patient's resting echocardiogram reading was normal. A preoperative transthoracic echocardiogram showed concentric left ventricular hypertrophy, an enlarged left atrium, and grade I diastolic dysfunction (impaired relaxation).

### What is the pathogenesis and treatment of hypertension?

Hypertension is one of the most common disorders in the adult population of developed countries, and the incidence is 30% in some parts of the world. The increase in the incidence of hypertension in the last 50 years has been dramatic. The precise cause of this increase is not known parallels the increase in the incidence of obesity. Obesity causes physiologic derangements such as sympathetic nervous system activation, insulin resistance, endothelial dysfunction, and increased aldosterone levels, all of which promote hypertension. Whether the two conditions are causally related or coincidentally related remains to be determined.

Although there are well-known specific causes of hypertension such as pheochromocytoma, primary aldosteronism, renovascular disease, and coarctation of the aorta, the specific cause of hypertension in most patients is unknown (essential hypertension). There are several mechanisms by which renal dysfunction causes hypertension: (a) reduced glomerular filtration rate that limits sodium excretion, (b) humoral disorders that increase sodium reabsorption, and (c) renal ischemia. Recently, it has been suggested that prolonged ingestion of fructose increases uric acid production, which in turn, activates the renin-angiotensin system, thereby increasing blood pressure.<sup>1</sup> More research will be required to fully delineate the different mechanisms that cause hypertension with the hope of developing specific treatment plans.

The traditional definition of hypertension is blood pressure greater than 140/90 mm Hg. The correlation between blood pressure and the incidence of myocardial ischemia and stroke is so strong that the definition of hypertension has been modified, and individuals with blood pressure greater than 120/80 but less than 140/90 mm Hg are considered to have pre-hypertension. Treatment of prehypertensive patients decreases the likelihood of ischemic heart disease.<sup>2</sup>

As more data have accumulated regarding the effects of different antihypertensive drugs on patient outcome, improved recommendations for treatment have developed. The ACE inhibitors and angiotensin receptor blockers (ARB) have been shown to be effective for a wide range of patients. Thiazide diuretics and calcium channel blockers are generally indicated for the initial treatment of uncomplicated hypertension.  $\beta$ -Adrenergic blockers are no longer considered to be a first line antihypertensive but are indicated for patients with ischemic heart disease and heart failure.<sup>3,4</sup> Therapy may also be guided by monitoring the effects of antihypertensives on secondary cardiac effects such as left ventricular hypertrophy with echocardiography.<sup>5</sup> Patients with hypertension are a very heterogeneous group, and therapy directed at reducing the impact of hypertension on end-organ function in an individual patient would be desirable (Tables 26.1 and 26.2).

### Should the patient's surgery be postponed because of elevated blood pressure?

The risks of anesthesia and surgery in a patient with hypertension include myocardial ischemia, stroke, renal dysfunction, and intraoperative blood pressure lability. Blood flow to most critical organs is autoregulated across a wide range of blood pressures. Chronically hypertensive patients can have altered autoregulatory responses, but it is difficult in an individual

**TABLE 26.1** Types of Hypertension

Type	Blood Pressure (mm Hg)
Normal	120/80
Prehypertension	130/85
Mild hypertension	140/90
Moderate hypertension	160/100
Severe hypertension	180/110
Very severe hypertension	210/120
Isolated systolic hypertension	Systolic blood pressure >140 mm Hg, diastolic blood pressure <90 mm Hg
Pulse pressure hypertension	Pulse pressure >65 mm Hg

patient to precisely define those altered autoregulatory responses. As anesthetics typically reduce blood pressure, the concern in hypertensive patients is whether the decrease in blood pressure reduces vital organ perfusion.

Studies performed in the 1960s and 1970s indicated that there was a significant perioperative risk of cardiac dysrhythmias and myocardial ischemia in hypertensive patients. Many of these patients, however, were not receiving any antihypertensive therapy. Most hypertensive patients today are receiving treatment, and the perioperative risks may not be as prevalent. The addition of many parenteral antihypertensive drugs for perioperative use has increased the anesthesiologist's ability to control blood pressure intraoperatively.

Current guidelines state that elective surgery in a patient with a blood pressure of 180/110 mm Hg or greater should have surgery postponed until better blood pressure control has been instituted. If urgent or emergent surgery is required, control can be instituted with rapid-acting antihypertensives.<sup>6</sup> These recommendations are based on the review of a number of studies that could not show a significant correlation between hypertension and adverse perioperative cardiac events. Despite liberalization of blood pressure values for surgery, patients with hypertension-induced end-organ damage such as ischemic heart disease, heart failure, renal disease, and cerebrovascular disease have an increased risk of adverse perioperative events.<sup>7</sup> Appropriate preoperative evaluation and perioperative management of these disorders is subsequently required.

As the patient's blood pressure was less than 180/110 mm Hg, and the evidence of end-organ damage was mild (diastolic dysfunction, left ventricular hypertrophy), it was decided to proceed with the surgery. The fact that the lung mass was most likely malignant conveyed some urgency for the surgery. The patient agreed to the insertion of a thoracic epidural catheter before induction for postoperative pain management. Sedation for epidural catheter insertion was achieved with the intravenous administration of 2 mg of midazolam and 50 mcg of fentanyl. After sedation, the patient's blood pressure

**TABLE 26.2** Treatment Recommendations for Hypertension

<55 years of age	ACEI
	ARBs
If additional therapy required, add CCB or diuretics	
>55 years of age	CCBs
(African descent, any age)	Diuretics (thiazide)
If additional therapy is required, add an ACEI or ARB. β-adrenergic blockers may be required for patients with ischemic heart disease or heart failure. Other antihypertensive drugs that may be required for treatment of resistant hypertension are spironolactone, vasodilators (hydralazine), and α-2 adrenergic agonists (clonidine). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.	

decreased to 135/85 mm Hg. A thoracic epidural catheter was placed without difficulty at T5.

### What are the goals for perioperative management of the patient with hypertension?

An accurate assessment of preoperative blood pressure is required so that perioperative blood pressure targets can be established. Anxiety (white coat hypertension) causes an elevation in blood pressure that does not accurately reflect the patient's steady state blood pressure. A review of serial blood pressure measurements from the medical records of the patient's primary care physician will provide a better blood pressure baseline. Blood pressure can be reduced with preoperative sedation and alleviation of anxiety. After the patient's "normal" blood pressure has been established, the goal during the perioperative period is to maintain blood pressure within 20% of normal. Postoperative analgesia with regional anesthesia may improve outcome after major surgery in hypertensive patients.<sup>8</sup> For the patient described in this case, a continuous thoracic epidural was selected as the technique of choice for postoperative analgesia. After establishing that the patient's normal blood pressure was 135/85 mm Hg (mean, 100 mm Hg), a target goal with a mean blood pressure of 80 to 100 mm Hg would be desirable.

Anesthesia was induced with propofol 1.5 mg/kg and rocuronium 0.8 mg/kg followed by positive pressure ventilation by mask with oxygen in sevoflurane followed by tracheal intubation with a 41-F left-sided double-lumen tube. After laryngoscopy and intubation, the patient's blood pressure was 210/120 mm Hg, and his heart rate was 94 beats per minute.

### Do patients with hypertension have intraoperative cardiovascular lability?

Hypertensive patients have a more active response to laryngoscopy and frequently demonstrate marked increases in blood pressure. The hypertensive response is more pronounced with prolonged laryngoscopy times. This response may be attenuated

with a number of different drugs such as  $\beta$ -blockers, opioids, dexmedetomidine, and vasodilators. Aggressive treatment may, however, result in hypotension. Whether blood pressure and heart rate lability influence outcome and whether outcome is worse in hypertensive patients is a complex issue. There is some evidence that tachycardia and hypertension are associated with adverse outcomes in patients undergoing prolonged surgery.<sup>9</sup> Whether better intraoperative control would have improved outcome is unknown. Today's anesthesiologist is much better equipped with a variety of drugs to control intraoperative hemodynamics than the anesthesiologist of 30 years ago.

Intravenous metoprolol was administered in incremental dosages of 1 mg (total dosage, 3 mg) to reduce the patient's heart rate, which declined to 71 beats per minute. His blood pressure decreased to 180/100 mm Hg. Intravenous nicardipine was administered in 1-mg increments (total dosage, 2 mg), and his blood pressure decreased to 125/75 mm Hg. Fifteen minutes after induction, the patient's blood pressure decreased to 80/50 mm Hg, and he did not respond well to ephedrine and phenylephrine.

### Does treatment of hypertension with ACE inhibitors and ARBs increase the likelihood of intraoperative hypotension?

Postinduction hypotension is more likely to occur in hypertensive patients treated with angiotensin receptor blockers as compared with hypertensive patients treated with  $\beta$ -adrenergic blockers or calcium channel blockers. Hypotension in this group of patients typically responds poorly to ephedrine and phenylephrine and is more responsive to vasopressin or terlipressin.<sup>10</sup> Whether angiotensin II antagonists and ACE inhibitors should be discontinued 24 hours before surgery is controversial.<sup>11</sup> This choice may be impractical and may lead to other unanticipated side effects. Such a recommendation is reminiscent of the recommendation for the discontinuation of  $\beta$ -adrenergic blockers preoperatively in the 1970s. A more rational approach may be to administer vasopressin initially or as soon as ephedrine and phenylephrine have proved ineffective.

A typical scenario in patients with hypertension is a significant increase in blood pressure with laryngoscopy that is treated with  $\beta$ -adrenergic blockers, vasodilators, or an increased inhaled concentration of volatile anesthetic. Aggressive treatment of post-laryngoscopy hypertension may result in hypotension once the stimulant effect of laryngoscopy has dissipated. The risk of hypotension may be reduced by the use of short-acting antihypertensives and somewhat less aggressive treatment.

### Although this patient did not exhibit isolated systolic hypertension, do elderly patients with this condition have an increased perioperative risk?

The aging process produces changes in the walls of large arteries that increase the stiffness and rigidity of the blood vessels. The loss of elasticity in the aorta causes an increase in systolic pressure, a decrease in diastolic pressure, and a subsequent increase in pulse pressure. Although the treatment of isolated systolic hypertension (ISH) was controversial, it is now accepted that there is an increased risk of morbidity and mortality from ISH and that treatment is indicated.<sup>12</sup> Treatment of elderly

patients with ISH, however, can be challenging and must be done with caution. An aggressive reduction of blood pressure can cause myocardial ischemia or cerebrovascular insufficiency.

Younger patients may exhibit systolic hypertension and an increased pulse pressure that has been termed *pulse pressure hypertension* (PPH). Although the causative mechanisms for PPH may be different from ISH, there is an increased risk of adverse postoperative cerebral and renal outcomes in patients with PPH.<sup>13</sup> Whether elective surgery should be postponed in patients with PPH or ISH remains to be determined.<sup>14</sup>

### KEY MESSAGES

1. Elective surgery in a patient with a blood pressure of 180/110 mm Hg or greater should have surgery postponed.
2. Intraoperative control of hemodynamics in hypertensive patients may be challenging.<sup>15</sup>
3. Postinduction hypotension is more likely to occur in hypertensive patients treated with angiotensin receptor blockers compared with hypertensive patients treated with  $\beta$ -adrenergic blockers or calcium channel blockers.
4. Aggressive treatment of post-laryngoscopy hypertension may result in hypotension once the stimulant effect of laryngoscopy has dissipated.

### QUESTIONS

1. What are the risks of anesthesia and surgery for patients with poorly controlled hypertension?

Answer: Risks include myocardial infarction, stroke, cardiac dysrhythmias, renal dysfunction, and perioperative blood pressure lability.

2. Why are  $\beta$ -adrenergic blockers no longer considered to be first line anti-hypertensive drugs?

Answer: Angiotensin receptor blockers (ARB) have been shown to be effective anti-hypertensives without the side effects of  $\beta$ -blockers, such as bradycardia, exercise and cold intolerance, and peripheral vasoconstriction.

3. What is the most effective treatment of intraoperative refractory hypotension in patients receiving preoperative angiotensin receptor blockers (ARB) and/or angiotensin converting enzyme (ACE) inhibitors?

Answer: Some patients receiving ARBs or ACE inhibitors can develop significant intraoperative hypotension. Vasopressin is more effective than ephedrine and/or phenylephrine.

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# Pharmacologic Myocardial Preconditioning

John Vullo

## CASE FORMAT: STEP BY STEP

A 73-year-old, 86-kg female presented for three-vessel off-pump coronary artery bypass grafting. She had been experiencing exertional angina and dyspnea increasing in severity for the 3 months before scheduled surgery. Coronary angiography revealed 90% occlusion of the right coronary artery and 70% occlusion of the left anterior descending and circumflex arteries. Her electrocardiogram demonstrated nonspecific ST-T waves changes and first-degree atrioventricular block (PR interval, 0.24). Trans-thoracic echocardiography showed inferior wall hypokinesis, impaired left ventricular relaxation, an enlarged left atrium, mild mitral regurgitation, and an ejection fraction of 45%. The patient had long-standing hypertension treated with daily valsartan and hydrochlorothiazide. Other medications included atenolol, simvastatin, and an over-the-counter medication for heartburn.

The patient's past surgical history included a cholecystectomy at 32 years of age and an abdominal hysterectomy at 68 years of age without known anesthetic complications.

The physical examination, including airway evaluation, was not remarkable. The patient's vital signs were as follows: blood pressure, 152/84 mm Hg; heart rate, 76 beats per minute; and respiratory rate, 16 breaths per minute. Room air arterial oxygen saturation by pulse oximetry was 95%. The laboratory testing values were as follows: hematocrit level, 38; hemoglobin level, 12.7 g/dL; creatinine, 1.0; potassium, 4.2; and sodium, 138.

The patient asked if anything could be done before her surgery to improve her cardiac outcome.

### What are the primary determinants of myocardial oxygen supply and demand?

Myocardial oxygen supply is determined by coronary blood flow and arterial oxygen content. Oxygen content is regulated by arterial oxygen saturation, oxygen tension, and hemoglobin as defined by the equation:

$$\text{CaO}_2 = 1.34 \times \text{hemoglobin} \times \text{O}_2 \text{ saturation} + 0.0031 \times \text{PaO}_2$$

Coronary blood flow occurs as a result of the pressure differential between aortic diastolic pressure and left ventricular end-diastolic pressure. An increase in left ventricular end-diastolic pressure or a decrease in aortic diastolic pressure can significantly decrease coronary blood flow and myocardial

oxygen supply. Two other important causes of decreased coronary blood flow are coronary artery stenosis and coronary artery spasm. Myocardial oxygen demand is dependent on heart rate, left ventricular contractility, and myocardial wall stress, as determined by afterload. The heart requires a 50% increase in blood flow for a doubling of any of these factors.

### What medications can be used to improve the balance between myocardial oxygen supply and demand?

Treatment of coronary artery disease must be individualized for each patient to provide medical and revascularization treatments that optimize myocardial oxygen supply and demand while preserving left ventricular function.<sup>1-3</sup>

There are several medications that can favorably influence myocardial oxygen supply and demand. Nitrovasodilators can decrease left ventricular pressures, decrease left ventricular afterload by decreasing systolic pressure, and increase coronary circulation through direct coronary artery and arteriolar dilation or reversal of spasm.  $\beta$ -Adrenergic blockers directly reduce myocardial oxygen consumption and improve coronary blood flow by prolonging the diastolic filling time. Calcium channel blockers decrease myocardial contractility and reverse coronary artery spasm. Ranolazine, a late sodium channel blocker, reduces diastolic wall stress, and antithrombotic agents maintain coronary artery patency by platelet inhibition. Statin drugs, generally used to reduce lipid levels, have also been found to reduce inflammation and oxidative stress.<sup>4</sup>

There are several clinical studies suggesting the efficacy of different medications that may reduce perioperative cardiac risk. Many of these studies lack the power to justify broad recommendations for the entire surgical population. The anesthesiologist must carefully evaluate each patient and individualize the anesthetic for each patient.

The enthusiasm for perioperative  $\beta$ -adrenergic blocker therapy has been tempered by the outcomes of the recently published results of the PeriOperative ISchemic Evaluation trial, which showed a decrease in the perioperative myocardial infarction rate but an increased risk of death and stroke in patients receiving long-acting metoprolol.<sup>5</sup>

### How did the patient's preoperative medical problems influence the selection of perioperative monitors?

The patient had significant coronary artery disease and long-standing hypertension with less-than-optimal control. The

standard intraoperative monitors used included a five-lead continuous electrocardiogram, capnography, and pulse oximetry. An indwelling radial artery catheter, central venous catheter, and a transesophageal echocardiograph (TEE) were also used. A pulmonary artery catheter was not inserted, as the TEE would provide more information about ventricular function, segmental wall motion, and ventricular filling.

### What induction drugs should be selected for this patient?

The goals of anesthesia for this patient are to reduce myocardial oxygen demand, provide adequate coronary filling pressure, and preserve left ventricular function. Concerns during induction include the potential for hypotension in a patient with mildly depressed left ventricular function and probable hypovolemia from chronic diuretic therapy. Induction of anesthesia should be performed in a slow, controlled manner by slow intravenous (IV) bolus injection or IV infusion. A BIS-guided IV infusion of propofol would accomplish those goals. Etomidate is a suitable alternative to propofol, although adrenal suppression continues to cause concern about the use of etomidate. Perhaps more important than the actual induction drug is the rapidity with which induction is performed.

Upon arrival in the operating room, a noninvasive blood pressure cuff, electrocardiogram, pulse oximeter, and BIS monitors were applied. Prior to the induction of anesthesia, IV sedation with midazolam (30 µg/kg) and fentanyl (1 µg/kg) was performed. A right radial arterial catheter was inserted with local anesthesia. Induction of anesthesia commenced with a propofol infusion at 600 µg/kg per minute and remifentanyl 0.25 µg/kg per minute until loss of consciousness was confirmed with loss of eyelash reflex and the BIS was 46. Rocuronium (0.8 mg/kg) was administered, and positive pressure ventilation was provided. The patient's trachea was intubated without difficulty with a 7.0-mm inner diameter orotracheal tube. After the tracheal intubation, her blood pressure was 115/75 mm Hg, and her heart rate was 68 beats per minute. The propofol infusion rate was decreased to 100 µg/kg per minute, and the remifentanyl infusion rate was decreased to 0.15 µg/kg per minute.

### Another anesthesiologist suggested that volatile, inhaled anesthetics produce myocardial ischemic preconditioning. What is ischemic preconditioning?

Myocardial preconditioning is a phenomenon that increases the heart's resistance to a period of ischemia. This protection persists after the intervention has taken place and has been removed. Methods relying on direct cardioprotection cease to provide protection once therapy is withdrawn. Ischemic preconditioning (IPC) was first described by Murry et al. in 1986.<sup>6</sup> IPC is elicited by exposing the heart to a brief episode or episodes of sublethal ischemia. A preconditioned heart that undergoes a subsequent period of prolonged ischemia will develop a much smaller infarct when compared with a nonconditioned heart. There are two phases to IPC, early and late. The early phase develops within minutes of ischemic exposure and lasts for 2 to 4 hours and is very effective for reducing lethal ischemia or infarct size. The late phase takes 24 hours to

develop and lasts for 3 to 4 days. The late phase has the unique property of reducing myocardial stunning following reperfusion as well as reducing infarct size. Preconditioning leads to the release of cellular substances including adenosine, bradykinin, and endorphins, which activate G protein-coupled receptors. Multistep processes activate signaling kinases, which maintain mitochondrial adenosine triphosphate (ATP) generation and inhibit apoptosis.<sup>7</sup>

Patients who have had anginal episodes preceding an infarct have better outcomes than those without antecedent angina. Repeated coronary occlusions during cardiac catheterization can decrease subsequent ischemic events for as long as 1 year. Intermittent cross-clamping of the aorta during cardiac surgery before cardiopulmonary bypass seems to provide some cardioprotection.

### Can anesthetics precondition the heart?

Many in vitro studies have shown the cardioprotective effects of volatile, inhaled anesthetics including halothane, enflurane, isoflurane, desflurane, and sevoflurane. Isoflurane and sevoflurane have been shown to reduce infarct size even when the volatile agent is discontinued prior to coronary artery occlusion. Proposed mechanisms for anesthetic-induced IPC include preservation of ATP, attenuation of inflammation, and reduced calcium loading. At the intracellular level, volatile anesthetics open mitochondrial ATP-sensitive K<sup>+</sup> (K<sub>ATP</sub>) channels and in turn, decrease mitochondrial energy consumption during ischemia (Table 27.1). Volatile anesthetics have also been shown to inhibit platelet aggregation, reduce myocardial damage, and decrease the likelihood of apoptosis during reperfusion after ischemia. The release of reactive oxygen species (ROS) during reperfusion depresses myocardial contractility. Volatile anesthetics reduce the release of ROS and attenuate or abolish neutrophil-induced myocardial depression.<sup>8</sup> Opioid agonists such as morphine and remifentanyl seem to enhance the protection of the myocardium achieved by anesthetic preconditioning. Studies of propofol and ketamine have produced conflicting results regarding myocardial preconditioning. Midazolam and etomidate do not affect

**TABLE 27.1** Proposed Mechanisms of Anesthetic Myocardial Preconditioning

Anti-inflammation
Reduced calcium loading
ROS
Decreased platelet adhesion
Improved ATP synthesis
Decreased neutrophil adhesion
Opening of K <sub>ATP</sub> channels (mitochondria)
ATP, adenosine triphosphate; K <sub>ATP</sub> , ATP-sensitive K <sup>+</sup> ; ROS, decreased reactive oxygen species.

**TABLE 27.2** Drugs That Affect Anesthetic Preconditioning

<b>Produce APC</b>
Halothane
Isoflurane
Enflurane
Sevoflurane
Desflurane
Opioids
Flumazenil
<b>Reduce APC</b>
Sulfonylureas
Glitazones
Cyclooxygenase-2 inhibitors
<b>No Effect on APC</b>
Midazolam
Etomidate
<b>Conflicting Evidence</b>
Propofol
Ketamine
APC, anesthetic preconditioning.

$K_{ATP}$  channels and do not produce anesthetic preconditioning (APC) (Table 27.2).

Hyperglycemia and diabetes may block the effects of IPC and APC. Sulfonylureas may also reduce the effectiveness of IPC and APC.

### Is APC clinically relevant?

Clinical studies of APC are difficult because of the many confounding variables such as altered hemodynamics, coexisting diseases, concomitant drug administration, and multi-drug anesthetic techniques. Several clinical studies, however, have produced compelling evidence that APC is clinically significant.<sup>9,10</sup> Clinical markers of improved outcome after coronary artery bypass grafting include reductions in the release of creatine kinase MB and troponins I and T, reduced incidence of dysrhythmias, and improved myocardial function.<sup>11,12</sup> It also appears that administration of volatile anesthetics is preferable throughout the intraoperative period rather than selected periods before and after ischemia.<sup>13</sup> In patients undergoing single-vessel off-pump coronary artery bypass grafting, both enflurane and a 5-minute period of ischemia/reperfusion preserved myocardial function and reduced free radical formation compared with a control group.<sup>14</sup>

After induction of anesthesia, the propofol was discontinued, and maintenance anesthesia was provided with remifentanyl (0.1  $\mu\text{g}/\text{kg}$  per minute) and a sevoflurane-oxygen mixture. During the maintenance phase of anesthesia, the patient's blood

pressure was 108/86 mm Hg, and her heart rate was 72 beats per minute. Brief periods of hypotension occurring during the grafting process were treated with intermittent doses of phenylephrine (1–2  $\mu\text{g}/\text{kg}$ ). After completion of the grafts, TEE showed no regional wall abnormalities and a left ventricular ejection fraction of 50% (Simpson's method). Postoperative sedation was provided with dexmedetomidine 0.5  $\mu\text{g}/\text{kg}$  per hour. The patient's trachea was extubated 3 hours after surgery.

There are many concerns for patients with coronary artery disease undergoing cardiac or noncardiac surgery. Optimal preoperative medical management of patients with ischemic disease has not yet been determined. Patients consequently present for surgery with a variety of drug regimens and recommendations from cardiologists. The results of new studies have confounded the attempts of large medical organizations to develop firm guidelines for the testing of patients with coronary artery disease undergoing noncardiac surgery. Frequent revisions of guidelines are required as the results of new studies appear.<sup>15</sup>

Appropriate monitoring of intraoperative cardiac function has been controversial for many years. The wealth of information provided by TEE exceeds what is possible with a pulmonary artery catheter. The TEE is relatively noninvasive, and the development of less expensive and more mobile echo units has increased convenience of use. Ischemic myocardial preconditioning of volatile anesthetics has produced a more balanced approach to anesthesia that uses volatile anesthetics in combination with opioids. The anesthesiologist must continue to develop perioperative management plans tailored to the individual's medical conditions.

### KEY MESSAGES

1. The PeriOperative ISchemic Evaluation trial demonstrated a decrease in the perioperative myocardial infarction rate but an increased risk of death and stroke in patients receiving metoprolol in the perioperative period.
2. Volatile anesthetics open mitochondrial  $K_{ATP}$  channels and decrease mitochondrial energy consumption during ischemia of the myocardium.
3. Anesthetic preconditioning is likely to be clinically significant.<sup>9,10</sup>

### QUESTIONS

1. What are the mechanisms by which anesthetics produce myocardial ischemic preconditioning (IPC)?  
Answer: The mechanisms include anti-inflammation, reduced calcium loading, reduction of reactive oxygen species (ROS), decreased platelet adhesion, and enhanced ATP synthesis.
2. What anesthetics have been shown to produce myocardial IPC?  
Answer: Anesthetics that produce myocardial IPC include isoflurane, sevoflurane, desflurane, and opioids.

## 3. Are there drugs that inhibit or reduce myocardial IPC?

Answer: Anti-diabetic drugs such as sulfonylureas and glitazones inhibit myocardial IPC.

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# Predicting Difficult Mask Ventilation

Stephen F. Dierdorf

## CASE FORMAT: REFLECTION

A 71-year-old, 5' 10", 106-kg male presented for a left carotid endarterectomy for carotid stenosis. Fifteen years before this procedure, he underwent successful coronary artery bypass surgery and has been free of cardiac symptoms since. He had a history of snoring at night and had intermittently used a continuous positive airway pressure machine. He had smoked one pack of cigarettes per day for 52 years. The patient's medications included metoprolol 50 mg daily and aspirin. His preoperative electrocardiogram reading showed nonspecific ST-T waves changes and sinus rhythm. The patient's blood pressure was 152/84 mm Hg, and his heart rate was 55 beats per minute. His airway examination showed Mallampati grade II, slightly decreased cervical extension, full beard present, and thyromental distance, 5 cm.

Monitors applied prior to induction included an electrocardiogram, a pulse oximeter, noninvasive blood pressure, and a 12-lead electroencephalogram. Anesthesia induction was achieved with midazolam 2 mg, fentanyl 100 µg, and propofol 100 mg. Rocuronium 70 mg was administered for muscle relaxation to facilitate tracheal intubation. After induction, mask ventilation was difficult but improved considerably after insertion of an oropharyngeal airway. Rigid direct laryngoscopy was attempted with a no. 3.5 Macintosh blade; only the tip of the epiglottis could be visualized. The oropharyngeal airway was replaced and mask ventilation continued. Two more attempts at rigid direct laryngoscopy were unsuccessful. Tracheal intubation was successful with a flexible fiberoptic scope and a 7.5-mm inner diameter tracheal tube. The surgical procedure was uneventful. At the conclusion of surgery, neuromuscular blockade was reversed with neostigmine 4 mg and 0.6 mg glycopyrrolate. Sustained tetanus was demonstrated with a peripheral nerve stimulator. The patient began to cough during emergence, and his trachea was extubated to avoid further increases in blood pressure. Arterial oxygen saturation at the time of extubation was 100%. The patient did not resume spontaneous ventilation after extubation, and positive pressure ventilation was not possible. An oropharyngeal airway was inserted, but there was no appreciable ventilation as evidenced by the lack of exhaled carbon dioxide and no chest movement. Arterial oxygen saturation decreased to 92%. An intubating laryngeal mask airway (LMA) was inserted, chest excursion was observed, and

exhaled carbon dioxide was detected. Oxygen saturation increased to 99%. After 5 minutes of assisted ventilation, the patient awakened, and the LMA was removed.

## DISCUSSION

This case illustrates several important features of airway management. The preoperative airway examination must evaluate several variables, as no single airway examination technique is reliable. Based on the findings for this patient, some difficulty in mask ventilation should have been anticipated. After induction of anesthesia, mask ventilation was difficult, but insertion of an oropharyngeal airway allowed satisfactory mask ventilation. Direct laryngoscopy proved to be difficult, and an alternative intubation technique using flexible fiberoptic laryngoscopy was required. The rapidity and ease with which the anesthesiologist changes from the primary technique to an alternative technique reduces the likelihood of an adverse airway event. At the conclusion of the case, extubation was premature, and mask ventilation was impossible until an intubating LMA was inserted. The importance of the airway during the emergence phase of anesthesia is often overlooked even in patients with known airway difficulty. There is often a desire to extubate patients at a deeper plane of anesthesia after head and neck surgery to avoid bleeding and excessive coughing. Depth of anesthesia is difficult to predict, and deep extubation requires careful planning to avoid serious consequences. If extubation is performed when the patient is not fully awake, there is a risk of laryngospasm and upper airway obstruction, especially in patients with sleep apnea.

Airway management is the single most important task for the anesthesiologist. It is also the greatest source of adverse outcomes in the practice of anesthesia.<sup>1</sup> Considerable research and development of new airway devices and techniques has occurred in the past 15 years. Difficult airway management is usually equated to tracheal intubation. Three notable publications that focused on the broad area of the difficult airway reported the incidence of difficult mask ventilation to be 0.07% to 1.4%.<sup>2-4</sup> Research specifically related to difficult mask ventilation, however, has been sparse. The importance of mask ventilation cannot be overemphasized, as it is the first technique used for ventilation after induction of anesthesia; it is a technique that has changed little in the past decades. A careful analysis of difficult airway management should separate mask ventilation and tracheal intubation, as the alternative techniques used for each are different.

The objective of the preoperative airway examination should be evaluation and assessment of the patient for both mask ventilation and tracheal intubation. Two studies predicted difficulty with mask ventilation in 1.56% to 5% of patients. Impossible mask ventilation occurred with a frequency of 1 in 600 to 1 in 1500 patients.<sup>5,6</sup> Predictive factors for difficult ventilation common to both studies were (a) history of snoring (? sleep apnea), (b) presence of a beard, (c) age greater than 55 to 57 years, and (d) a body mass index >26 to 30 kg/m<sup>2</sup>. Other factors reported in the studies but not common to both or measured by both were (a) limited mandibular protrusion, (b) lack of teeth, and (c) a thyromental distance less than 6 cm. Differences in findings among studies may be secondary to variations in the definition of difficult mask ventilation. The American Society of Anesthesiologists Practice Guidelines for Management of the Difficult Airway defines difficult mask ventilation as:

1. It is not possible for the unassisted anesthesiologist when using 100% oxygen to maintain the arterial oxygen saturation greater than 90% in a patient whose arterial oxygen saturation was greater than 90% before induction of anesthesia.
2. It is not possible for the unassisted anesthesiologist to prevent or reverse signs of inadequate ventilation during positive pressure ventilation. Signs of inadequate ventilation include cyanosis, absence of exhaled carbon dioxide, absence of breath sounds and chest movement, and hemodynamic changes associated with hypoxemia and hypercarbia<sup>7</sup> (Table 28.1).

The Difficult Airway Society Guidelines from the United Kingdom focus on unanticipated difficult intubation and have little information concerning mask ventilation.<sup>8</sup> Since the initial publication of the American Society of Anesthesiologists difficult airway guidelines in 1993, subsequent studies of difficult mask ventilation have used more liberal definitions of

**TABLE 28.1** Preoperative Airway Evaluation

**History**

Preoperative respiratory conditions

Smoking

Snoring

Obstructive sleep apnea

Age

**Physical Examination**

Mallampati classification

Cervical range of motion

Mouth opening

Condition of teeth and bite

Thyromental distance

Presence or absence of a beard

Body mass index

Neck circumference

**TABLE 28.2** Grading Scale for Mask Ventilation

Grade 0:	Mask ventilation not attempted
Grade 1:	Ventilation by mask
Grade 2:	Mask ventilation with pharyngeal airway
Grade 3:	Difficult mask ventilation (inadequate, unstable, two-person)
Grade 4:	Unable to mask ventilate

Data from Han R, Tremper KK, Kheterpal S, et al. Grading scale for mask ventilation. *Anesthesiology* 2004;101:267.

difficult mask ventilation by increasing the lower limit of arterial oxygen saturation (92%) and developing a grading system for mask ventilation. The clinical benefit of a stricter definition of difficult mask ventilation is earlier intervention with an alternative technique, thereby reducing the risk of an adverse outcome (Table 28.2).

Mask ventilation is only one part of airway management. Mask ventilation is, however, of considerable importance, as it is the first technique used after a patient loses consciousness. If ventilation with a face mask is adequate, even if tracheal intubation is difficult, there is time to initiate alternative airway management techniques. Inadequate ventilation resulting in hypoxemia reduces the amount of time available for use of alternative techniques. Airway evaluation predictive of difficult mask ventilation, consequently, is important to permit accessibility to other devices and techniques.

The supralaryngeal airways, most notably the LMA, have led to change in how difficult ventilation is defined. Because supralaryngeal airways are extremely effective for ventilation in difficult situations, the definition of *difficult ventilation* is determined by the inability to establish ventilation with a supralaryngeal airway rather than by face mask. Anesthesiologists must be highly skilled in the use of the LMA, and anesthesia training programs have a responsibility to ensure that each trainee is thoroughly versed in the use of the LMA. There are two learning phases for the LMA. The first phase requires 50 to 75 uses and allows the user to learn the rudiments of the LMA and establish ventilation in healthy patients. The second phase requires several hundred uses to develop skills for reliably managing patients with difficult airways.

**SUMMARY**

Airway management is the most important task that an anesthesiologist performs. At the conclusion of formal training, anesthesiologists are experts at airway management of healthy patients. True expertise for managing the difficult airway requires considerable experience and skill development. A complete preoperative airway examination is a poor predictor of airway outcome. Preoperative airway evaluation, however, does provide the anesthesiologist with an indicator of what alternative techniques may be required for a specific patient.

The anesthesiologist must be skilled with several alternative techniques and should be able to smoothly and quickly move from one technique to another when the clinical situation arises. Unless there is a specific contraindication, extubation with the patient fully awake can avoid several potential airway problems in patients with a history of obstructive sleep apnea.<sup>10</sup>

### KEY MESSAGES

1. The airway examination is a multivariate exercise with poor predictive power.
2. Difficult mask ventilation and difficult intubation are different entities.
3. The anesthesiologist must be skilled in alternative airway techniques.
4. Tracheal extubation has risks similar to those associated with intubation.

### QUESTIONS

1. Complications with what organ system contribute to the greatest likelihood of adverse outcomes related to the practice of anesthesia?

Answer: Respiratory system complications produce the highest incidence of adverse outcomes during the course of anesthesia.

2. What are the predictive factors for difficult mask ventilation?

Answer: Predictive factors for difficult mask ventilation include a history of snoring, presence of a beard, body mass index of  $>30$ , and age greater than 55 years.

3. What is the most appropriate procedure for impossible mask ventilation of a morbidly obese patient?

Answer: Insertion of a supraglottic airway (e.g., LMA) would be the most appropriate method for ventilation of a morbidly obese patient should mask ventilation fail.

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# Awake Tracheal Intubation

Stephen F. Dierdorf

## CASE FORMAT: STEP BY STEP

A 64-year-old, 74-kg male with laryngeal cancer presented for laryngectomy and right radical neck dissection. The patient complained of hoarseness, dysphagia, and dyspnea when supine that had increased in severity over the previous 3 months. He had declined surgery 6 months before the current scheduled surgery. The patient had smoked 2 packs of cigarettes per day for 44 years. The ear, nose, and throat surgeon's consultation noted that there was a large mass originating from the right false vocal cord, and the cross-sectional area of the glottic inlet was reduced by 65%. The mass extended into the anterior tracheal wall, and there was a significant reduction of epiglottic mobility.

The patient's past medical history included an inferior wall myocardial infarct followed by off-pump three-vessel coronary artery bypass grafting at 61 years of age. Since the coronary artery bypass grafting, he had been free of chest pain; however, dyspnea from the laryngeal cancer had restricted his physical activity. An open cholecystectomy had been performed at age 44 without known anesthetic complications. He has had a long-standing history of hypertension treated with angiotensin-converting enzyme inhibitors. The patient's vital signs were as follows: blood pressure, 145/85 mm Hg; heart rate, 84 beats per minute; respiratory rate, 22 breaths per minute; and the room air oxygen saturation was 91%. The preoperative airway examination showed decreased cervical range of motion and decreased mouth opening. There was a hard 8-cm fixed mass in the right neck, and there was stridor with forced inspiration.

### How should the patient's airway be managed for anesthesia induction?

The patient had several airway abnormalities such as decreased cervical range of motion, poor mouth opening, and an obstructive laryngeal mass that make awake, tracheal intubation the best option. Induction of general anesthesia before intubation increases the risk of further airway obstruction in a patient that may be difficult to ventilate and perform rigid, direct laryngoscopy for tracheal intubation. Insertion of a supraglottic airway after induction of anesthesia does not guarantee a patent airway in a patient with significant laryngeal pathology. The overall clinical presentation of this

patient when integrated with the American Society of Anesthesiologists guidelines for management of the difficult airway leads to the logical recommendation for awake, tracheal intubation.<sup>1</sup>

### How should the patient be prepared for awake, tracheal intubation?

Patient preparation begins with a thorough explanation regarding the importance of performing intubation while awake. A frank discussion of the potentially dire consequences of the lost airway after anesthesia induction and the necessity of an awake intubation will do much to convince the patient of the merits of awake intubation. The patient must also be assured that his comfort during the procedure is of paramount importance, and a variety of methods including parenteral sedation and topical and/or regional anesthesia will be used to make him comfortable.

The innervation of the upper airway is extensive and is provided by several nerves. Branches of the trigeminal nerve supply the nasal cavity, and the glossopharyngeal nerve provides sensation to much of the pharynx, while the vagus nerves provide sensory innervation to the larynx via the superior laryngeal nerves. The gag reflex is controlled by the vagus nerves.<sup>2</sup> A single nerve block that provides complete upper airway anesthesia is, consequently, not possible. Techniques for regional anesthesia include glossopharyngeal nerve block (oropharynx), superior laryngeal nerve block (larynx above the vocal cords), and transtracheal block (larynx below the vocal cords). Regional nerve blocks may be technically challenging and less reliable in patients with distorted anatomy secondary to tumor growth and tissue infiltration.

Either the nasal or oral route can be selected for fiberoptic intubation. Unless the procedure specifically requires nasotracheal intubation, the oral route is preferred. Nasal intubation is associated with a higher likelihood of complications such as epistaxis, sinusitis, and bacteremia. Passage of a tracheal tube through the nasal passage is more uncomfortable for the patient because the pressure sensation as the tracheal tube compresses the soft tissue of the nasal passage against bony structures is difficult to attenuate.

After the patient arrived in the preoperative holding area, the anesthesiologist provided a thorough explanation of the plan for awake, tracheal intubation. Glycopyrrolate (0.1 mg intravenous [IV]) was administered. The patient was instructed to slowly and deeply inhale 4% lidocaine via a nebulizer. After inhaling the lidocaine, the patient was transferred to the operating room.



Pharyngeal secretions retard diffusion of the local anesthetics across the membranes of the upper airway. An antisialogogue will dry mucous membranes and improve the quality of topical anesthesia. In comparison to atropine, glycopyrrolate produces comparable drying of secretions with less risk of tachycardia or central nervous system side effects. Inhalation of topical anesthetic will disperse the medication throughout the upper airway. This initial phase of upper airway anesthesia can be done in the holding area without parenteral sedation.

After transfer to the operating room, parenteral sedation was initiated with midazolam (30  $\mu\text{g}/\text{kg}$ ) and fentanyl (1  $\mu\text{g}/\text{kg}$ ). An IV infusion of dexmedetomidine (0.7  $\mu\text{g}/\text{kg}$  per hour) was begun. Before sedation, the patient's heart rate was 86 beats per minute, and his blood pressure was 150/85 mm Hg. After sedation, his heart rate was 71 beats per minute, and his blood pressure was 120/75 mm Hg.

The level of sedation must be closely monitored to avoid oversedation that increases the likelihood of airway obstruction and apnea. Low-dose midazolam produces amnesia without excessive sedation. Fentanyl provides additional sedation and suppresses the cough reflex. Dexmedetomidine, a short-acting  $\alpha_2$  adrenergic agonist provides sedation without significant respiratory depression.<sup>3,4</sup> Dexmedetomidine can be administered as a continuous infusion (0.7  $\mu\text{g}/\text{kg}$  per hour) or as a loading dose (1  $\mu\text{g}/\text{kg}$ , ideal body weight). Rapid infusion of dexmedetomidine can cause bradycardia and hypotension. Although sedation techniques have been described for each of these drugs independently, the higher doses of a single drug increase the likelihood of complications. Combining the drugs in lower doses produces a comfortable patient without respiratory depression. To obtain an optimal level of sedation, proper timing of sedative administration and adequate time to achieve effect are required.

After a satisfactory level of sedation has developed, additional topical anesthetic can be applied to the tongue, oropharynx, and hypopharynx. Many different methods can be used that employ commercially available products and dispensing devices.<sup>5</sup> Lidocaine ointment can be applied to the under surface (tongue contact side) of an intubating airway. The airway is slowly advanced over the patient's tongue and into the pharynx; as the ointment is warmed, it liquefies and coats the mucous membranes of the oropharynx and hypopharynx. Once the airway has been inserted to maximal depth and the patient is comfortable, a flexible fiberscope can be passed through the airway, and additional topical anesthetic is instilled through the working channel of the fiberscope (Table 29.1).

### Which device or technique should be used for intubation?

Every technique for tracheal intubation has been used for awake intubation. The development of new devices and techniques for intubation in the past 15 years has increased the anesthesiologist's options for intubation of the patient with a difficult airway. Technique selection depends on the type of airway abnormality and the likelihood of success without complications. For this patient with a laryngeal mass, it is valuable to inspect the relationship of the mass to the laryngeal inlet without undue trauma. Blind insertion of any device incurs the risk of trauma to the tumor and displacement of the mass into a more obstructive position. A high-resolution

**TABLE 29.1** Patient Preparation for Awake, Tracheal Intubation

Thorough explanation of the purpose
Explanation of the process
Administration of an antisialogogue
Inhalation of local anesthetic
Parenteral sedation
Direct application of topical anesthetic
Insertion of an intubating oral airway
Fiberscope insertion
Fiberscope navigation
Passage of tracheal tube

flexible fiberscope allows the anesthesiologist to visualize the larynx without altering the position of the mass with little risk of trauma. The working channel of the fiberscope provides a route for instillation of additional local anesthetic to the laryngeal inlet and the trachea.<sup>6</sup>

Satisfactory sedation and topical anesthesia of the oropharynx was achieved. An Ovassapian intubating airway was slowly inserted into the oropharynx with minimal discomfort to the patient. A 5.2-mm video bronchoscope with a preloaded 6.0-mm inner diameter tracheal tube was passed through the patient's airway and into the hypopharynx. Oxygen at 4 L/min was insufflated via the working channel. At the level of the epiglottis, 2 mL of 4% lidocaine was injected through the working channel. Instillation of the lidocaine provoked mild coughing; no further advance of the fiberscope was attempted until the coughing subsided. After the patient's coughing ceased, the fiberscope was advanced under the epiglottis and into the glottic inlet where 2 mL of 4% lidocaine was instilled through the working channel. Slight coughing developed that quickly subsided, the fiberscope was advanced into the subglottic region, and another 2 mL of 4% lidocaine was administered via the working channel. No coughing occurred with the final lidocaine instillation, and the fiberscope was advanced into the midtrachea. After confirmation of the fiberscope position in the midtrachea, the well-lubricated tracheal tube was advanced over the fiberscope and into the trachea. The tracheal tube cuff was gently inflated, and tracheal intubation was confirmed by capnograph. General anesthesia was induced with IV propofol and inhaled sevoflurane.

There are two basic types of flexible fiberscopes in clinical use. The older optical type fiberscopes contain an imaging bundle of optical fibers through which the endoscopist views the airway. Optical fiberscopes are limited in resolution, magnification, and field of view by the number of fibers in the imaging bundle and are subject to some optical aberration. A camera can be attached for image display on a monitor. The camera, however, does not alter the resolution or field of view. The second and more modern type of fiberscope, the flexible videoscope, has a charged-coupled device (CCD) chip at the end of the scope that transmits a digital signal to a microprocessor

that constructs an image on a monitor. Videoscopes provide high-resolution, wide-angle images that are superior to the images of an optical fiberscope. Videoscopes are preferred for use in patients with upper airway tumors or when there is blood in the airway. The wide-angle field of view displays the laryngeal tumor in relationship to the entire hypopharynx. Proper fiberscope selection to meet the requirements of the clinical situation improves the efficiency and success rate for awake, tracheal intubation.

If the endoscopist is patient and recognizes anatomical landmarks before advancing the fiberscope, this will permit methodic manipulation of the scope and navigation through the airway. Instillation of local anesthetic through the working channel of the fiberscope at the levels of the epiglottis, laryngeal inlet, subglottis, and midtrachea enhances patient comfort and cooperation. If the local anesthetic provokes coughing, the scope should not be advanced until the local anesthetic has taken effect and the coughing has ceased. Oxygen insufflated through the working channel blows secretions away from the end of the fiberscope and reduces lens fogging. Direct observation of the airway pathology provides important diagnostic information that may alter the plan for airway management.

### What are the potential complications from awake, fiberoptic tracheal intubation?

The complication rate for awake, fiberoptic tracheal intubation is extremely low.<sup>7</sup> There are sporadic case reports of infrequent complications that may be a result of the endoscopist's inexperience or lack of patient cooperation. Care must be taken to avoid oversedation and apnea that can lead to urgent airway management in a patient with a difficult airway. Local anesthetic toxicity rarely occurs in adult patients, but the local anesthetic dosage must be carefully controlled for young children. Passage of the fiberscope or tracheal tube can provoke laryngospasm and/or bronchoconstriction. Adequate airway anesthesia usually prevents such airway responses. The fiberscope should be gently passed, as forceful insertion may traumatize the airway.

Oxygen insufflation through the working channel of the fiberscope has been reported to cause gastric distention. This is an extremely rare event, although the patient's abdomen should be observed periodically for any evidence of distention (Table 29.2).

**TABLE 29.2** Potential Complications of Awake, Tracheal Intubation

Oversedation
Local anesthetic toxicity
Gastric distention
Airway obstruction
Laryngospasm
Bronchoconstriction
Airway trauma

### Does the availability of supraglottic airways eliminate the need for awake, tracheal intubation?

There is little doubt that the invention and development of supraglottic airways has reduced the need for awake, tracheal intubation.<sup>8,9</sup> This is especially true for situations in which external abnormalities (e.g., cervical spine abnormalities) limit airway access or in children with congenital airway abnormalities (e.g., Pierre-Robin, Treacher-Collins, Klippel-Feil syndromes). For patients with immediate supralaryngeal or intralaryngeal pathology (e.g., tumors, direct trauma), direct visualization of the lesion provides important information concerning airway management. The need for awake, tracheal intubation is still present for the anesthesiologist, as there are still situations in which awake, tracheal intubation may prevent significant morbidity and mortality.<sup>10,11</sup>

### KEY MESSAGES

1. Patient preparation for awake, tracheal intubation begins with a thorough explanation of the importance and need for the procedure.
2. Regional nerve blocks performed to facilitate awake, fiberoptic intubation may be technically challenging and less reliable in patients with distorted anatomy secondary to tumor growth and tissue infiltration.
3. For a patient with a laryngeal mass, it is valuable to inspect the relationship of the mass to the laryngeal inlet without causing undue trauma.
4. Compared with (older) optical fiberscopes, flexible videoscopes are preferred for patients with upper airway tumors or when there is blood in the airway.

### QUESTIONS

1. Why does administration of an antisialagogue (e.g. glycopyrrolate) improve the quality of topical airway anesthesia for awake, tracheal intubation?

Answer: Pharyngeal secretions impede the diffusion of topical anesthetics across mucous membranes. Drying of secretions enhances the quality of topical anesthesia.

2. What cranial nerves provide sensation to the upper airway?

Answer: Sensory input to the upper airway is supplied by the trigeminal, glossopharyngeal, and vagus nerves.

3. Why do videoendoscopes produce a higher resolution image than optical endoscopes?

Answer: Resolution and field of view of an image provided by an optical endoscope are determined by the number of fibers in the imaging bundle. A bundle with more fibers produces an image of higher resolution. A videoendoscope uses a CCD chip instead of an optical imaging bundle.

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# Is There a Future for Succinylcholine?

Stephen F. Dierdorf

## CASE FORMAT: REFLECTION

A 26-year-old woman presented for an emergency laparoscopic appendectomy. Her medical history is unremarkable, and she has not had previous surgery. She began having abdominal pain 48 hours before admission to the hospital. She had eaten a breakfast of toast and scrambled eggs 2 hours before arrival in the emergency department. Preoperative examination revealed normal upper airway anatomy and normal cardiorespiratory systems. Laboratory measurements including a complete blood count and serum electrolytes were normal other than an elevated white blood count.

The patient's overall health status was very good, and there was nothing in her medical history to suggest any potential interactions between systemic diseases and anesthesia.

The primary consideration is a patient with a full stomach for an emergency procedure. The main goal during the induction period was to intubate the trachea and isolate the airway from the gastrointestinal tract as quickly as possible to minimize the risk of regurgitation and aspiration of gastric contents. The choice of a hypnotic induction drug for this patient was not critical. The selection of a muscle relaxant to facilitate tracheal intubation was a more important choice. Should the choice be succinylcholine or a nondepolarizing muscle relaxant? The advantages of succinylcholine are rapid, predictable onset and short duration of action. For this young woman, the risk of myalgia and the possibility of serious, unpredictable side effects of succinylcholine led to the selection of cisatracurium as the muscle relaxant of choice.

In the operating room, standard preinduction monitors (electrocardiogram, automated blood pressure device, pulse oximeter) were placed. Prior to induction, midazolam 3 mg and fentanyl 100  $\mu$ g were administered intravenously, and preoxygenation was performed for 3 minutes. Anesthesia induction was performed with propofol 2 mg/kg and cisatracurium 0.1 mg/kg. As soon as the patient was unconscious, an assistant applied cricoid pressure, and positive pressure ventilation with oxygen and sevoflurane was carried out. Two minutes after administration of cisatracurium, direct laryngoscopy was done. After the laryngoscope was inserted, the patient retched, and gastric contents were seen to enter the trachea. The trachea was quickly intubated, and positive pressure ventilation with 100% oxygen was performed. Arterial oxygen saturation declined to 82. Despite

positive pressure ventilation and 5 cm of positive end-expiratory pressure, arterial oxygen saturation remained in the low-to-mid 80s. An arterial blood gas showed a PaO<sub>2</sub> of 62 with an inspired oxygen fraction of 1.0. After the appendectomy was completed, the patient was transferred to the intensive care unit, and mechanical ventilation was continued. She was extubated without difficulty 30 hours after surgery.

## DISCUSSION

### What is the risk of perioperative pulmonary aspiration?

Older studies report the incidence of aspiration in patients receiving general anesthesia as 1 per 2000 to 3000. A more recent study reported the incidence to be 1 in 7000. Whether this decrease represents a true reduction in the incidence of aspiration is not clear. Aspiration is more likely to occur during emergency surgery and in patients with significant coexisting diseases. Although the overall risk of death from perioperative aspiration is low (1 in 35,000–99,000), patients who do aspirate have a 50% chance of developing a respiratory complication and a 5% to 7% chance of dying. The relative infrequency of perioperative pulmonary aspiration should not allow anesthesiologists to become complacent about its risks.<sup>1,2</sup>

### Is there a standardized rapid sequence induction?

The introduction of curare into clinical practice in 1942 ushered in a new era in anesthesiology. Muscle relaxation could then be produced with specific muscle relaxants without having to use high doses of inhaled anesthetics. At that time, curare was used as an adjunct to anesthesia and not specifically for tracheal intubation. The introduction of succinylcholine in the 1950s provided anesthesiologists with a drug that produced rapid, profound muscle relaxation suitable for tracheal intubation. Succinylcholine became central to the evolution of the technique for rapid sequence induction (RSI) to minimize the risk of aspiration pneumonitis in patients with a full stomach. The term *rapid sequence induction* has been defined by the era during which the anesthesiologist trained and was never truly standardized. The classic RSI consisted of preoxygenation for 3 to 5 minutes, pretreatment with a small dose of a nondepolarizing muscle relaxant

(prevention of fasciculation and increased intragastric pressure), administration of an induction hypnotic, cricoid pressure as soon as the patient was unconscious, administration of succinylcholine, no positive pressure ventilation by mask, and tracheal intubation. There have been many modifications to this sequence with respect to mask ventilation and type of muscle relaxant. Routine use of the pulse oximeter demonstrated how quickly arterial oxygen saturation can decline in a patient presenting for emergency surgery. Mask ventilation is now often performed when the patient becomes apneic. Cricoid pressure is regarded as optional, as it can provoke retching and emesis and may obstruct the upper airway. Pediatric anesthesiologists have significantly modified the RSI technique by substituting rocuronium for succinylcholine and using gentle positive pressure ventilation.<sup>3</sup> Children with normal pulmonary compliance can be easily ventilated with a peak airway pressure of 10 to 12 cm water. Although the list of side effects from succinylcholine is lengthy, and newer muscle relaxants have challenged its indications, succinylcholine is still widely used inside and outside the operating room to facilitate rapid tracheal intubation.<sup>4</sup>

### Are there suitable alternatives to succinylcholine?

There is no doubt that the use of succinylcholine has been restricted with the availability of short-acting nondepolarizing muscle relaxants such as rocuronium and cis-atracurium. To produce rapid profound relaxation with these drugs, however, requires four times the ED<sub>95</sub> resulting in a long recovery period.

Side effects from succinylcholine began to be recognized soon after its widespread use became common practice. These side effects include prolonged apnea (pseudocholinesterase deficiency), myalgia, rhabdomyolysis, masseter spasm, increased intraocular pressure, increased intragastric pressure, hyperkalemia, bradycardia, and a trigger for malignant hyperthermia. After a cause-and-effect relationship was established between succinylcholine and a side effect, methods to avoid the side effect were aggressively pursued. The ability to prevent or attenuate these side effects has prolonged the use of succinylcholine for many years. Rocuronium has emerged as the most useful of the nondepolarizing muscle relaxants for rapid tracheal intubation if succinylcholine is contraindicated. Although rocuronium compares favorably to succinylcholine regarding rapidity of onset and creating situations favorable for tracheal intubation, the dose of rocuronium (1–1.5 mg/kg) required to produce the best conditions for intubation results in a long duration of action.<sup>5–7</sup> Studies performed in pediatric patients show a more favorable comparison between rocuronium (0.9–1.2 mg/kg) and succinylcholine (1.5 mg/kg) with respect to onset of action and intubation conditions.<sup>8,9</sup> Time to recovery at those doses of rocuronium is 40 to 45 minutes. If rocuronium in higher doses is comparable to succinylcholine, the greatest challenge to succinylcholine use may not be another muscle relaxant, but a reversal drug: sugammadex. Sugammadex is a biologically inactive cyclodextrin that is a highly specific antagonist to rocuronium. If sugammadex proves to be as effective as initial studies indicate, succinylcholine will become used less

**TABLE 30.1** Side Effects of Succinylcholine

Fasciculation
Myalgia
Increased intragastric pressure
Increased intraocular pressure
Increased intracranial pressure
Hyperkalemia
Malignant hyperthermia
Bradycardia
Rhabdomyolysis
Masseter spasm
Prolonged apnea (cholinesterase deficiency)

often. Proof of sugammadex's efficacy without significant side effects will only come after widespread clinical use. Rapacuronium was touted as the replacement for succinylcholine, and it was not until the drug was released for general clinical use that rapacuronium-induced bronchospasm was reported with increasing frequency. The frequency and severity of the bronchospasm led to its withdrawal from clinical practice.

### What is the role of succinylcholine in modern anesthetic practice?

Succinylcholine has been in continuous clinical use for nearly 60 years. It has been a life-saving drug when rapid tracheal intubation has been required. Although succinylcholine has accumulated an extensive list of minor and major side effects, it is still a valuable muscle relaxant in the anesthesiologist's pharmacologic armamentarium. The most important indications for the use of succinylcholine are RSI and when profound relaxation is required for a short period of time. The indications for succinylcholine depend on several factors relative to the clinical situation and the concern for possible side effects. Absolute contraindications to succinylcholine use include patients with postburn injury, spinal cord transection, susceptibility to malignant hyperthermia, and patients with primary myopathies. Most other contraindications are relative, and the risk of complications must be weighed against the benefits of rapid tracheal intubation (Table 30.1). There are techniques for reducing the incidence and severity of some of the side effects of succinylcholine. Fasciculation and myalgia may be attenuated by pretreatment with one of several drugs, including lidocaine, nonsteroidal anti-inflammatory medications, or a small dose of nondepolarizing muscle relaxant (Table 30.2).<sup>10</sup>

The future for succinylcholine is unclear. The highly specific antagonist for rocuronium, sugammadex, may make succinylcholine obsolete. Other drugs, however, have failed to relegate succinylcholine to historical annals. The combination of rocuronium and sugammadex will require extensive clinical use before it replaces succinylcholine. Until that time, succinylcholine will still be in use.

**TABLE 30.2** Drugs That Reduce Post-Succinylcholine Myalgia

Defasciculating dose of a nondepolarizing muscle relaxant Pancuronium, rocuronium, vecuronium, atracurium Side effects: blurred vision, heavy eyelids, diplopia, dyspnea
Sodium channel blockers (lidocaine)
Nonsteroidal anti-inflammatory drugs
Benzodiazepines (weak effect)

## SUMMARY

The patient in this case was undergoing emergency surgery and was considered to have a full stomach and to be at risk for aspiration pneumonia based on the time of her last oral intake and probable delayed gastric emptying from appendicitis.

Cisatracurium is slow and unpredictable in onset compared with succinylcholine and rocuronium. Paralysis was incomplete when direct laryngoscopy was attempted, and the patient retched and vomited. Succinylcholine or rocuronium would have been a better choice for muscle relaxation. Stimulation with a peripheral nerve stimulator before direct laryngoscopy would have undoubtedly shown incomplete paralysis, and aspiration could have been avoided.

## KEY MESSAGES

1. Patients requiring emergency surgery are at increased risk for aspiration pneumonitis.
2. There are suitable alternatives for succinylcholine for elective surgery.
3. Succinylcholine may still be the most suitable muscle relaxant for RSI.
4. Positive pressure ventilation should be rapidly instituted after aspiration occurs.

## QUESTIONS

1. If succinylcholine is contraindicated for a rapid sequence induction, what muscle relaxant produces satisfactory conditions for tracheal intubation in the shortest period of time?

Answer: Rocuronium has the most rapid onset of effect of the non-depolarizing muscle relaxants currently available for clinical use and is a suitable alternative to succinylcholine.

2. Why are patients with primary myopathies more likely to develop hyperkalemia after the administration of succinylcholine?

Answer: Patients with primary myopathies such as Duchenne muscular dystrophy have abnormal muscle membranes that are fragile and susceptible to damage from depolarization. Disruption of muscle membranes results in the release of large amounts of potassium from the muscle cytoplasm into the circulation.

3. Pretreatment with what types of drugs prevents or attenuates succinylcholine-induced myalgia?

Answer: Pretreatment with a defasciculating dose of a non-depolarizing muscle relaxant, lidocaine, or nonsteroidal anti-inflammatory drugs has been shown to reduce the incidence of myalgia after succinylcholine.

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# Cuffed Tracheal Tubes for Children

Stephen F. Dierdorf

## CASE FORMAT: REFLECTION

A 7-year-old, 35-kg girl presented for repair of an aortic coarctation and ventricular septal defect. Although she was asymptomatic, a systolic heart murmur was detected during a routine physical examination. She is quite active physically while playing competitive soccer and gymnastics. Previous surgery included bilateral myringotomies at 2 years of age as well as a tonsillectomy and adenoidectomy at 4 years of age. The parents reported no complications from previous anesthesia other than nausea and vomiting. The patient's preoperative vital signs were as follows: temperature, 37.0°C; right arm blood pressure, 145/85 mm Hg; right leg blood pressure, 80/50 mm Hg; heart rate, 92 beats per minute; and respiratory rate, 18 breaths per minute. A grade II/VI systolic heart murmur was present. Satisfactory preoperative sedation was achieved with oral midazolam 0.5 mg/kg administered 30 minutes before induction. Anesthesia was induced with sevoflurane in oxygen. After induction, an intravenous catheter was inserted into a vein in the patient's right forearm, and a cannula was inserted into the right radial artery. Muscle relaxation was achieved with 0.5 mg/kg of rocuronium, and the trachea was intubated with a 6.0-mm uncuffed orotracheal tube. Positive pressure ventilation demonstrated a large leak around the tracheal tube (12 cm water [H<sub>2</sub>O]). The tracheal tube was replaced with a 6.0-cuffed orotracheal tube; 3 mL of air injected into the pilot balloon produced an air seal. Anesthesia maintenance was performed with nitrous oxide (N<sub>2</sub>O) and sevoflurane in oxygen and a continuous infusion of remifentanyl 0.3 µg/kg per minute. The surgical procedure and separation from cardiopulmonary bypass were uneventful. The patient was transferred directly to the intensive care unit. She was weaned from mechanical ventilation and extubated 4 hours after admission to the intensive care unit. Thirty minutes after extubation, she developed inspiratory stridor that was not relieved by inhaled racemic epinephrine and intravenous dexamethasone. She was reintubated with a 5.5-mm inner diameter uncuffed tracheal tube. There was no audible leak around the 5.5-mm tracheal tube. Tracheal extubation was attempted 12 hours later with similar results, and the patient was reintubated. An ear, nose, and throat surgeon recommended that microlaryngoscopy and bronchoscopy should be performed under general anesthesia in the operating room. Laryngoscopy and bronchoscopy revealed tracheal wall edema, erythema, and mucosal ulceration at

the site of the tracheal tube cuff. The patient was extubated 36 hours after bronchoscopy. Three months after surgery, she presented with dyspnea. Bronchoscopy performed with general anesthesia showed a stenotic area at the midtrachea (Fig. 31.1).

## DISCUSSION

### What are the advantages of a cuffed tracheal tube?

Cuffed tracheal tubes permit an air seal between the tracheal tube and the tracheal wall. The seal permits controlled positive pressure ventilation without a leak and loss of inspired volume. The leak around an uncuffed tracheal tube is hard to control, and as pulmonary or chest wall compliance decreases, effective ventilation diminishes, and the risk of aspiration of gastric and pharyngeal contents around the tracheal tube increases. Leakage of exhaled carbon dioxide will give a falsely low end-tidal carbon dioxide reading. Other advantages of cuffed tracheal tubes include more reliable low-flow anesthesia, less need for tracheal tube replacement, and reduced operating room pollution with trace anesthetic gases.

### Are children more vulnerable to postintubation complications?

The controversy surrounding the use of cuffed tracheal tubes in pediatric patients has persisted for decades.<sup>1</sup> Many pediatric anesthesiologists recommend that cuffed tracheal tubes should not be used in children younger than 8 years of age. This recommendation is based on the anatomy of the child's larynx and trachea. The infant larynx is vertically compact, the epiglottis is short, and the aryepiglottic folds are thick. The glottis is 7 mm in the anteroposterior axis and 4 mm in the lateral axis. The narrowest dimension of the neonatal airway is 4 to 5 mm at the subglottis. The cricoid ring has a thick submucosa with abundant mucus-producing glands. From birth to 3 years of age, there is rapid proportional growth of the larynx. The anatomic relationships of the laryngeal structures are therefore, constant.<sup>2</sup> Tracheal mucosal edema produces a proportionately larger decrease in the cross-sectional area of the child's trachea compared with the adult. Tracheal wall pressure exceeding 30 cm H<sub>2</sub>O in adults may compromise perfusion of the tracheal wall causing ischemia and permanent tracheal damage. Tracheal perfusion pressure in young children is undoubtedly



**Figure 31.1 • Endoscopic View of Tracheal Stenosis.**

less than for the adult. The air leak test is commonly used to determine optimal tracheal tube fit. If a leak is present at 25 cm H<sub>2</sub>O, fewer postoperative adverse respiratory events have been reported.<sup>3</sup> The air leak test, however, may not be as predictive of postextubation stridor in children younger than 7 years of age.<sup>4</sup> N<sub>2</sub>O can diffuse into the tracheal tube cuff and increase the intracuff pressure to high levels. The rate of diffusion and subsequent pressure increase depends on the surface area for gas exchange, the permeability of the cuff material, and the thickness of the cuff<sup>5</sup> (Table 31.1).

The pediatric airway is vulnerable to injury at three levels: the glottic inlet, the cricoid (subglottis), and the midtrachea. Examination of children after prolonged tracheal intubation frequently reveals damage to the posterior commissure where the tracheal tube usually rests, at the level of the cricoid, and in the trachea from pressure against the tracheal wall. The ideal tracheal tube would be as narrow as possible at the levels of the vocal cords and cricoid, but it would be able to produce an air seal in the trachea. The uncuffed tube that produces a reasonable seal in the trachea may be too large at the level of the glottis and the cricoid. A cuffed tube may be closer to ideal if the cuff is thin, properly fitted for the child's airway, and exerts a low pressure against the tracheal wall at a "just seal" volume or slightly lower.

The consequences of intubation injury can be minor such as hoarseness or more serious, requiring reintubation and long-term therapy. The administration of dexamethasone to reduce mucosal edema and inflammation has been and remains controversial; however, most pediatric anesthesiologists and otolaryngologists use dexamethasone in clinical practice.<sup>6</sup>

### Can tracheal tubes be designed specifically for children?

Detailed analyses of currently available tracheal tubes have shown considerable variation among manufacturers regarding depth of insertion, outer wall thickness, cuff position on the tube, and cuff thickness.<sup>7</sup> Most currently available pediatric tracheal tubes lack the careful design and precision manufacturing that might greatly reduce the incidence of postintubation side

**TABLE 31.1** Impact of Airway Edema on Cross-Sectional Area

Adult			
Cricoid diameter (mm)	Area	Area (1-mm edema)	Decrease
20	31.4 mm <sup>3</sup>	25.4 mm <sup>3</sup>	19%
Infant			
5	19.6 mm <sup>3</sup>	7.06 mm <sup>3</sup>	61%

effects. The relationship between tracheal tube placement and complications is far more complex in children than adults. Most pediatric tracheal tubes are merely smaller versions of adult tracheal tubes, and the design is not based on pediatric anatomy. There is no standardization for pediatric tracheal tubes. Tracheal tube wall thickness and cuff thickness vary among manufacturers and among different tubes from the same manufacturer. Cuff position relative to the tip of the tracheal tube varies greatly. The problems presented by poor design include long cuffs and a substantial increase in outer tracheal tube diameter by thick cuffs.<sup>8</sup> In extreme cases, the proximal cuff may rest at the level of the cricoid or the glottic inlet, while the tip of the tube is in the midtrachea.

The development of a new type of tracheal tube specifically designed for children may herald a new era in pediatric tracheal tubes. The Microcuff Paediatric Tracheal Tube (Microcuff GmbH, Weinheim, Germany) employs a very thin (10 μ) polyurethane low-pressure cuff that is placed distally on the tracheal tube. Intracuff pressures at "just seal" average 11 cm H<sub>2</sub>O for the Microcuff tube compared with 21 to 36 cm H<sub>2</sub>O for more conventional tracheal tubes.<sup>9,10</sup> Currently, most of the studies done with this tracheal tube have been published by the same group, and confirmation of these studies is needed. The design of this tracheal tube is theoretically sound and provides a template for other manufacturers to follow.

Routine tracheal tube cuff pressure monitoring or the use of an automated pressure relief valve may be indicated for any cuffed tracheal tube. Precise pressure monitoring eliminates the assumption that pressure is satisfactory.<sup>11</sup>

## SUMMARY

This case illustrates several important concepts about tracheal intubation and tracheal tubes in children. Cuffed tracheal tubes in pediatric patients can be used and have several advantages. Great care, however, must be taken to ensure that there is no excessive pressure on the tracheal wall. Arbitrary inflation volumes for tracheal tube cuffs are to be discouraged, as the cuff pressure is unknown. Diffusion of N<sub>2</sub>O into the cuff can markedly increase the intracuff pressure. It is unfortunate for this patient that she had an excellent surgical result but is left with a serious postintubation complication that will require extensive therapy. The development of pediatric-specific tracheal tubes may reduce the likelihood of complications in the future.



**KEY MESSAGES**

1. The use of cuffed endotracheal tubes in children is highly controversial.
2. N<sub>2</sub>O diffusion into the tracheal tube cuff can markedly increase intracuff pressure and increase the risk of tracheal wall ischemia.
3. The leak test may not predict adverse airway events after extubation.
4. Pediatric tracheal tubes need to be specifically designed for children.

**QUESTIONS**

1. How does the anatomy of the infant airway at the laryngeal level differ from the anatomy of the adult airway?

Answer: The adult airway is cylindrical in shape with the narrowest area at the level of the vocal cords. The infant larynx is cone shaped and the narrowest area is at the level of the cricoid cartilage.

2. What is the impact of airway edema on the cross-sectional area of a pediatric airway?

Answer: Inflammation of the airway lining produces a comparable amount of edema in both adults and children. The reduction in cross-sectional area caused by inflammatory edema can be three to four times greater in the infant as compared to the adult.

3. Does the inhalation of nitrous oxide increase the pressure and volume in a tracheal tube cuff?

Answer: Nitrous oxide diffuses into air filled cavities much faster than nitrogen can diffuse out of the cavity. If the cavity is non-expandable, the intracavity pressure will

increase. The trachea is a relatively rigid tube and the intracuff pressure will increase as nitrous oxide diffuses into the cuff.

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# Role of Intraoperative BIS Monitoring

Stephen F. Dierdorf

## CASE FORMAT: STEP BY STEP

A 45-year-old, 97-kg male was scheduled to undergo a laparotomy for colon cancer resection. He had a history of mild hypertension that was controlled with 100 mg of losartan per day. He had undergone no prior surgery and had no allergies. The patient's heart rate was 66 beats per minute, and his blood pressure was 124/78 mm Hg. He was concerned about the safety of anesthesia and asked the anesthesiologist a few questions.

### How safe is anesthesia, and what monitors will be used during my surgery?

The safety of anesthesia has improved dramatically in the past 30 years. Increased safety can be attributed to increased knowledge of pathophysiology, the introduction of better anesthetic drugs, and the development of more and better monitors. All patients receiving anesthesia are observed with standard monitors such as a continuous electrocardiograph, pulse oximeter, blood pressure cuff, and capnograph. These monitors are considered to be the standard of care by most regulatory and professional anesthesiology organizations. The primary function of these required monitors is the evaluation of cardiorespiratory function during the perioperative period. An optional monitor that may be used is a device that watches neurologic function to monitor effects of the anesthetic and detect cerebral ischemia. Although there are several neurologic monitors available, the BIS monitor (Aspect Medical Systems, Newton, MA) is the most frequently used. Other neurologic monitors in clinical use include the SEDline (Hospira, Lake Forest, IL), the Narcotrend (Schiller AG, Baar, Switzerland), Entropy (GE Healthcare, UK), the Cerebral State Monitor (Danmeter A/S, Odense, Denmark), and the AEP/2 Monitor (Danmeter, Odense, Denmark).

### How does the BIS monitor work, and what does it measure?

The electroencephalograph (EEG) measures a complex signal of brain electrical activity. Continuous monitoring of multiple channels of the raw EEG is not practical in the operating room for the anesthesiologist. Signal processing techniques to render the EEG more informative have been developed in recent years. These processing techniques break the EEG signal into a family of sinusoids with three basic elements: amplitude, frequency, and phase angle. Most processing methods

analyze power and frequency. Bispectral analysis adds additional information that examines the phase relationships of the sinusoids. The bispectral index is a dimensionless number based on processing of the EEG with bispectral analysis and clinical information. The BIS of the awake patient is 90 to 100. Moderate hypnosis is indicated by a number of 60, and deep hypnosis is indicated by 40 (Fig. 32.1).<sup>1-3</sup>

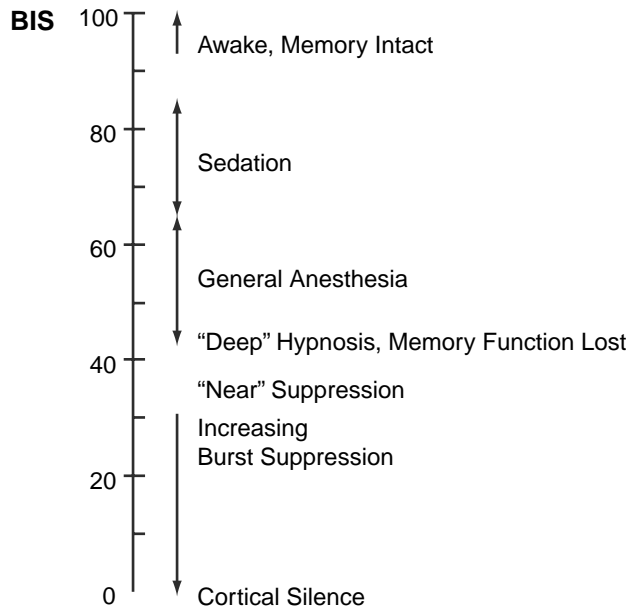
The clinical purpose of BIS monitoring is to determine the level of hypnosis during sedation and general anesthesia with the hope of more precise administration of anesthetic drugs. *Depth of anesthesia* is a difficult term to define and cannot be represented by a single monitor. Depth of anesthesia incorporates hypnosis, analgesia, and reflex responses. The neural function that has gained the most attention with respect to monitoring is intraoperative awareness. Whether routine BIS monitoring reduces the incidence of awareness is controversial.<sup>4,5</sup>

The patient was brought to the operating room. The electrocardiogram, blood pressure cuff, pulse oximeter, and BIS sensor were applied before the induction of anesthesia. Anesthesia was induced with 2.5 mg/kg of propofol, and 0.8 mg/kg of rocuronium was administered to provide muscle relaxation for tracheal intubation. Positive pressure ventilation with sevoflurane in oxygen was provided until muscle relaxation was achieved. Three minutes after the administration of propofol, the patient's blood pressure was 70/45 mm Hg with a heart rate of 58 beats per minute. The BIS was 9.

### Can routine BIS monitoring reduce the incidence of hypotension during induction?

Administering an induction drug by an intravenous bolus technique is based on an assumption of how much drug each patient will require. Variability of individual patient drug response would suggest that such assumptions are not always accurate, and the rate of drug administration may influence hemodynamic responses.<sup>6</sup> A carefully titrated drug administration based on BIS response reduces the risk of a relative drug overdose and subsequent hypotension.<sup>7</sup> A BIS index of less than 40 is frequently associated with hypotension. Slow administration of the induction drug either by small bolus injections or continuous infusion to a BIS index of 50 produces a satisfactory level of anesthesia with less decrease in blood pressure and heart rate. This is especially evident in geriatric patients.

The sevoflurane concentration was decreased, and 5 mg of ephedrine was given intravenously. Within 2 minutes, the patient's blood pressure increased to 105/70 mm Hg, and the BIS increased to 50.



**Figure 32.1 • The Bispectral Index Scale.**

### What BIS number (value) is consistent with adequate hypnosis during the maintenance phase of anesthesia?

There is no precise BIS number that is consistent with an adequate level of hypnosis during anesthesia maintenance. In general, a range of 50 to 60 seems desirable. Titration of maintenance anesthesia with isoflurane to a range of 50 to 60 produces faster recovery in elderly patients.<sup>8</sup> There is concern that consistently low BIS levels (<45) may be associated with adverse outcomes.<sup>9</sup> This study has been highly controversial and requires confirmation. Elderly patients (>60 years) seem to have an increased risk of long-term postoperative cognitive dysfunction after major noncardiac surgery.<sup>10</sup>

Routine BIS monitoring during anesthesia has been shown to reduce anesthetic consumption, time to extubation, nausea and vomiting, and recovery room time.<sup>11,12</sup> Prediction of emergence may be influential in avoiding immediate postoperative respiratory complications. If the patient attains clinical evidence of recovery and the BIS is >90, there seems to be minimal risk of airway obstruction and laryngospasm.

There is considerable anecdotal experience that profound decreases in the BIS index may indicate cerebral ischemia. These case reports describe a variety of clinical scenarios such as cardiac arrest, hypotension, anaphylaxis, or cardiac dysrhythmias that may decrease cerebral perfusion. The BIS level usually decreases to less than 10 but increases if cerebral perfusion returns in a timely manner. Whether the rapid return of the BIS to normal anesthetic ranges after a period of cerebral hypoperfusion has prognostic significance is as yet undetermined.

At the conclusion of surgery, residual neuromuscular blockade was reversed with neostigmine, 0.07 mg/kg and

**TABLE 32.1** Perioperative Neural Monitors

BIS monitor
SEDLine (Hospira, Lake Forest, IL)
AEP Monitor/2 (Danmeter, Odense, Denmark)
Entropy (GE Healthcare, UK)
Cerebral State Monitor (Danmeter A/S, Odense, Denmark)
Narcotrend (Schiller AG, Baar, Switzerland)

glycopyrrolate, 0.01 mg/kg. Sustained tetanus was demonstrated with a peripheral nerve stimulator. The patient opened his eyes upon command, the BIS was 94, and the trachea was extubated. His immediate postoperative course was normal. An anesthesiology colleague asked whether routine BIS monitoring should be required.

### Should routine BIS monitoring be required?

Function of the central nervous system is complex, and currently available monitors are primitive in comparison. The BIS monitor is not the only available neural monitor, and others may offer advantages that have not yet been fully researched. When properly used and interpreted, the BIS monitor can provide information that allows the anesthesiologist to provide improved management of anesthesia. The BIS monitor has been used to a greater extent than any previous neural monitor, but it should most likely be regarded as a first step in the development and clinical application of routine neural monitoring to the practice of anesthesiology.<sup>13,14</sup> The designation of a monitor as a standard monitor introduces an extensive list of regulatory and legal requirements that may imply a greater value to the monitor than it actually has.

Neural monitors of the future should give very specific information about the functional status of the patient's central nervous system and the integrity of cerebral perfusion and metabolism. The development of advanced neural monitors should assist anesthesiologists with actually defining and measuring the depth of anesthesia (Tables 32.1 and 32.2).

**TABLE 32.2** Advantages of Routine BIS Monitoring

Reduce incidence of awareness
More predictable emergence
Decreased time to extubation
Less nausea and vomiting
Improved nursing utilization
Teaching tool

## KEY MESSAGES

1. The bispectral index is a dimensionless number based on processing of the EEG with bispectral analysis and clinical information.
2. Depth of anesthesia incorporates hypnosis, analgesia, and reflex responses.
3. Routine BIS monitoring during anesthesia has been shown to reduce anesthetic consumption, time to tracheal extubation, nausea and vomiting, and recovery room time.
4. The BIS monitor is not the only available "depth of anesthesia" monitor, and others may offer advantages that have not yet been fully investigated.

## QUESTIONS

1. What variables of the electroencephalograph (EEG) does bispectral analysis process?

Answer: Bispectral evaluates and processes power, amplitude, and phase relationships. This analysis technique evaluates more parameters than most processed EEG programs.

2. What range of BIS values is desired during the maintenance phase of anesthesia?

Answer: During the maintenance phase of anesthesia, the desired BIS range is 50 to 60. It may not, however, be possible to consistently achieve a specific range in clinical practice.

3. What are the potential benefits of the routine use of the BIS monitor?

Answer: The goal of monitoring the effects of anesthesia on the central nervous system is to precisely administer the proper amount of anesthetic drug(s) to avoid over or under-dosing. A BIS-guided anesthetic may reduce the

incidence of intraoperative hypotension, postoperative nausea and vomiting, immediate postoperative respiratory complications, and reduce recovery time.

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# Duchenne Muscular Dystrophy and Volatile Anesthetics

Stephen F. Dierdorf

## CASE FORMAT: STEP BY STEP

A 4-year-old, 17-kg male was scheduled for bilateral inguinal hernia repair and a muscle biopsy. His pediatrician suspected that the child had Duchenne muscular dystrophy (DMD). His only prior surgery was strabismus surgery at 2 years of age performed with general anesthesia without any known complications. The suggestion that their child may have muscular dystrophy was recent, and the boy's parents asked the anesthesiologist to tell them about the disease.

### What is DMD?

The cytoskeleton of the muscle cell is composed of a complex of proteins such as dystrophin, dystroglycan, sarcoglycan, utrophin, syntrophin, and dystrobrevin (Fig. 33.1). Dystrophin is the largest of the proteins and the most critical component of the dystrophin-glycoprotein complex. This complex links the cell membrane to the contractile elements of the muscle cell and stabilizes the membrane during contraction. Patients with DMD have a mutation in the gene that regulates dystrophin production, and they lack dystrophin. The absence of dystrophin increases the fragility of the muscle membrane rendering it prone to damage and release of intracellular contents into the circulation. Skeletal muscle biopsies from patients with DMD demonstrate various stages of muscle cell necrosis, regeneration, and ultimately replacement of contractile muscle with adipose and fibrotic tissue. DMD is a sex-linked recessive trait that is clinically evident in males. Progressive muscle weakness produces symptoms between the ages of 2 and 5 years with significant limitation of mobility by 12 years of age. Sequential serum creatine kinase (CK) levels reflect the disease's progression. Early in the patient's life, CK levels are elevated. As the patient ages and significant amounts of skeletal muscle have degenerated, CK levels decrease. Although skeletal muscle weakness produces the earliest and most obvious clinical abnormalities, cardiac and smooth muscle are affected as well. Loss of myocardial muscle, as reflected by a progressive decrease in R-wave amplitude on the electrocardiogram with aging, results in dilated cardiomyopathy, dysrhythmias, and mitral regurgitation. Echocardiography with tissue Doppler imaging and myocardial strain measurement can reveal subtle changes in myocardial function before the onset of symptoms.<sup>1,2</sup> Smooth muscle involvement causes gastroparesis, delayed gastric emptying, and an increased risk of aspiration.

Diminished skeletal muscle strength produces an ineffective cough that can lead to retention of pulmonary secretions and pneumonia. Death is secondary to congestive heart failure or pneumonia.

Despite identification of the gene defect that causes DMD more than 20 years ago, the pathophysiology is poorly understood, and specific therapy has remained elusive.<sup>3</sup> Studies of gene therapy in a DMD (*mdx*) mouse model have begun. Corticosteroids increase muscle strength and improve cardiorespiratory function.<sup>4</sup> Afterload reduction with angiotensin-converting enzyme inhibitors can improve cardiac function and increase ejection fraction.  $\beta$ -adrenergic blockers may also be efficacious but may cause cardiac conduction changes.

There are other types of muscular dystrophy (Table 33.1). Becker muscular dystrophy (BMD) most closely resembles DMD. Patients with BMD usually have some dystrophin, and the clinical course is milder with onset of symptoms later (11 years) and a longer life expectancy. BMD patients can develop a severe dilated cardiomyopathy.

The parents reported nothing unusual in their son's medical history, and his only previous anesthetic at age 2 was uneventful.

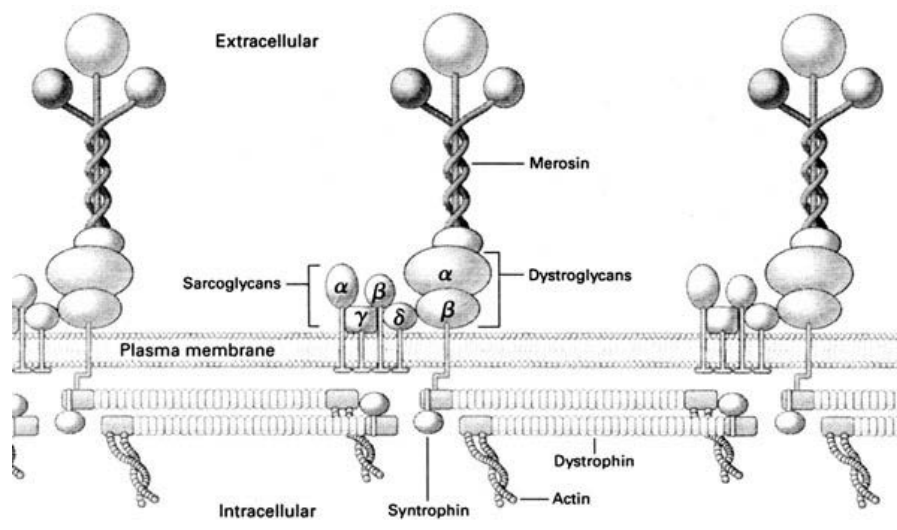
### What information should be obtained from the preoperative evaluation?

Many children with DMD are asymptomatic, and the clinical features may be subtle during the early stages of the disease. First-time parents may be unaware of developmental milestones and are unable to report evidence of delayed motor development. The anesthesiologist must be alert for any signs of skeletal muscle dysfunction such as hypotonia, delayed walking and speech, gait disturbances, or pseudohypertrophy of muscles (gastrocnemius). An elevated CK level may be the first evidence of DMD. A preoperative cardiology consultation and echocardiography are recommended for patients with suspected or known DMD.

The parents were somewhat overwhelmed about the suspected diagnosis of DMD and were also concerned about the likelihood of an adverse event.

### What are the risks of anesthesia?

A small (<20 cases) but steady accumulation of case reports of adverse effects in patients with DMD has developed during the past 2 decades.<sup>5</sup> The cases, in varying degrees, show evidence of severe rhabdomyolysis, hyperkalemia, metabolic acidosis, hyperthermia, renal failure, coagulopathy, and frequently death (Table 33.2). The similarity of this clinical complex and



**Figure 33.1 • Muscle Cell Cytoskeleton.** (Reproduced with permission from Duggan DJ, Gorospe JR, Fanin M, et al. Mutations in the sarcoglycan genes in patients with myopathy. *N Engl J Med* 1997;336:618–624. Copyright 1997 Massachusetts Medical Society. All rights reserved.)

malignant hyperthermia (MH) led to the suggestion that DMD patients are susceptible to MH. Studies in *mdx* mice have failed to establish any link between DMD and MH. The term applied to the aforementioned clinical complex in patients with DMD is *anesthesia-induced rhabdomyolysis* (AIR). The development of AIR is unpredictable, and many patients with DMD have received volatile anesthetics and succinylcholine without apparent ill effects. The unpredictability of AIR may be related to the timing of the anesthetic exposure relative to the ongoing disease process. Patients who have had a previous uneventful anesthetic may develop AIR during subsequent exposures. AIR can occur during the anesthetic, during early recovery, or during late recovery from anesthesia.<sup>6</sup>

The parents reported that their child is extremely fearful of needles and becomes hysterical when receiving injections. They insisted on an inhalation induction before an intravenous line (IV) is placed.

Twenty-five minutes before the planned induction, 0.5 mg/kg of midazolam in 5 mL of acetaminophen elixir was administered orally for preoperative sedation. After transfer to the

operating room, routine monitors were applied. Anesthesia induction was performed with 8% sevoflurane in oxygen. A 22-gauge IV catheter was inserted into a vein on the dorsum of the child's right hand. Rocuronium 0.3 mg/kg was administered, and positive pressure ventilation with 3% sevoflurane in oxygen was performed without difficulty. The patient's trachea was intubated with a 5-mm inner diameter orotracheal tube and surgery commenced. Ten minutes after the start of surgery, the T waves on the electrocardiogram began to peak. The peaked T waves were quickly followed by an increased duration of the QRS complex and ventricular tachycardia. An arterial blood gas sample revealed  $FiO_2$ , 1.0;  $PaO_2$ , 412;  $PaCO_2$ , 54; pH, 7.20; BE, -6; and potassium, 9.0 mEq/L. The patient's temperature was 38.2°C. IV lidocaine (1 mg/kg) and bicarbonate (0.5 mEq/kg) were administered without effect, and cardiopulmonary resuscitation was initiated. Calcium gluconate, 20 mg/kg was administered, and the ventricular tachycardia converted to a sinus tachycardia of 140 beats per minute. A Foley catheter was

**TABLE 33.1** Types of Muscular Dystrophy

Duchenne
Becker
Emery-Dreifuss
Oculopharyngeal
Fascioscapulohumeral
Congenital
(Ulrich, Walker-Warburg)

**TABLE 33.2** Clinical Features of Anesthesia-Induced Rhabdomyolysis

Rhabdomyolysis
Hyperkalemia
Tachycardia
Ventricular dysrhythmias
Metabolic acidosis
Hyperthermia
Renal dysfunction
Coagulopathy

inserted, and the patient's urine was noted to be dark red. Another blood gas sample obtained 30 minutes after the first revealed PaO<sub>2</sub>, 402; PaCO<sub>2</sub>, 45; pH, 7.37; BE, 0; potassium, 4.5 mEq/L; and CK level, 21,500. Tetanic stimulation of the ulnar nerve showed moderate fade. Neostigmine (70 µg/kg) and glycopyrrolate (10 µg/kg) were administered for reversal of neuromuscular blockade. Twenty minutes after the administration of neostigmine, tetanus was sustained, and the trachea was extubated after the child was fully awake. He was transferred to the intensive care unit for close observation. The postoperative course was uneventful, and the patient was discharged to home after 36 hours.

A muscle biopsy performed 1 month after the initial anesthetic was diagnostic for DMD. Anesthesia for the muscle biopsy was performed with IV ketamine, propofol, and remifentanyl.

### What is the best treatment for AIR?

The most immediate threat to the patient with AIR is acute hyperkalemia, and the plasma potassium level may exceed 12 mEq/L. The characteristic electrocardiogram changes from acute hyperkalemia progress rapidly from peaked T waves to a prolonged QRS complex, to a severely prolonged QRS complex, to ventricular tachycardia, to ventricular fibrillation. The best initial treatment of acute hyperkalemia is IV calcium (20 mg/kg). For the patient with acute transient hyperkalemia seen with AIR, one dose of calcium is generally sufficient. If hyperkalemia persists, another dose of calcium can be administered and an infusion of insulin and glucose begun. The risk of renal dysfunction from deposition of myoglobin in the renal tubules can be reduced with hydration and the administration of mannitol. Serial arterial blood gas measurements are valuable for treatment of acidosis and electrolyte abnormalities.

### Are volatile anesthetics contraindicated in patients with DMD?

Whether volatile, inhaled anesthetics are contraindicated in patients with DMD is controversial. The unpredictability of AIR prevents scientifically based recommendations, but the severity of AIR suggests avoidance of volatile anesthetics.<sup>7-9</sup> It can be speculated that younger patients with DMD may be more likely to develop AIR because muscle tissues are undergoing both necrosis and regeneration. Later in life (adolescence) when muscle becomes fibrotic, there may be less likelihood of AIR. The presence of cardiomyopathy, which is more likely in adolescents with DMD, increases the possibility of severe myocardial depression from volatile anesthetics.

The predictability of AIR is unlikely until there is a better understanding of how the pathophysiology of DMD can produce adverse effects from anesthetics. Volatile anesthetics are best avoided but if needed, should be used judiciously, for as short a time as possible, and with alertness for the development of AIR.

### Are muscle relaxants contraindicated for patients with DMD?

Succinylcholine is contraindicated for patients with DMD.<sup>10</sup> Nondepolarizing muscle relaxants have been used without

adverse effects. The response to nondepolarizers may, however, be abnormal. Studies with rocuronium indicate that the onset of peak neuromuscular blockade is delayed and that recovery is prolonged.<sup>11,12</sup> Reversal with anticholinesterase inhibitors (neostigmine, pyridostigmine) can generally be achieved, but careful monitoring of neuromuscular function is necessary.

### KEY MESSAGES

1. DMD is an insidious disease with subclinical abnormalities that cause changes in skeletal, cardiac, and smooth muscle.
2. Volatile anesthetics can produce life-threatening rhabdomyolysis with acute hyperkalemia, myoglobinuria, and fever that may mimic MH.
3. The best initial therapy of acute hyperkalemia is the administration of IV calcium.

### QUESTIONS

1. What is the best immediate therapy for succinylcholine-induced hyperkalemia with cardiac dysrhythmias?

Answer: The best immediate therapy for succinylcholine-induced hyperkalemia is the intravenous administration of calcium. At the cardiac cell level, calcium is a direct antagonist to potassium. Since the hyperkalemia is transient, one dose of calcium is generally sufficient.

2. What is anesthesia-induced rhabdomyolysis (AIR)?

Answer: AIR is a clinical complex that occurs in patients with primary myopathies (Duchenne muscular dystrophy) characterized by rhabdomyolysis, acidosis, hyperkalemia, and hyperthermia. AIR can be triggered by succinylcholine and inhaled, volatile anesthetics. Although AIR resembles malignant hyperthermia, AIR is probably a different entity.

3. Why is the muscle membrane of patients with Duchenne muscular dystrophy (DMD) fragile and easily damaged?

Answer: The cytoskeleton of the muscle membrane is a complex of large proteins that protect and maintain the integrity of the muscle cell. Patients with DMD lack dystrophin a major component of the cytoskeleton. The muscle membrane consequently lacks the strength of normal membranes and can be damaged by excessive depolarization.

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# Anesthesia for Magnetic Resonance Imaging

Stephen F. Dierdorf

## CASE FORMAT: STEP BY STEP

A 4-month-old, 4.2-kg male was scheduled for an outpatient cranial magnetic resonance imaging scan (MRI) because of an irregular breathing pattern and possible focal seizures. He was born preterm at 34 weeks postconceptual age and required a stage I Norwood procedure for hypoplastic left heart syndrome. He was discharged to home 2 weeks after surgery and has been feeding and growing well since discharge. The patient's vital signs were as follows: heart rate, 130 beats per minute; blood pressure, 85/54 mm Hg; respiratory rate, 28 breaths per minute; and room air arterial oxygen saturation, 77%. The mother asked the anesthesiologist a few questions as follows.

### How does anesthesia for an MRI differ from anesthesia in the operating room?

The physical environment in the MRI suite is much different from the environment in the operating room.<sup>1</sup> Magnetic fields generated in the MRI magnet are quite strong compared with the earth's magnetic field. The gauss (G) and the tesla (T) are units of magnetic field strength. One tesla equals 10,000 gauss. The strength of the earth's magnetic field is 0.6 G. Clinical MR field strengths are 0.5 to 3 T. Magnetic fields of greater than 3 T are used for research, but in coming years, they may be used clinically. The ever-increasing magnetic strengths used for clinical imaging complicate determination of suitability for equipment in the magnetic environment.

The MRI area has been divided into four zones depending on the proximity to the magnet and the strength of the magnetic field (Table 34.1). The intense magnetic field in the MRI suite is not compatible with standard anesthesia machines and monitors. Any magnetic object in the field may become a projectile as the object is drawn into the magnet. Serious injuries have been reported in patients and personnel struck by magnetic objects. A strong handheld magnet (1000 G or greater) should be available for preliminary testing of equipment for potential magnetic attraction. Patients with implanted ferromagnetic objects may be at risk for injury or damage to the device from the strong magnetic field. The current classification places metallic objects into one of three categories: (a) MR safe, (b) MR conditional, and (c) MR unsafe. The safety of MR imaging of patients with implanted cardiovascular devices is controversial. Correct identification of the device and a risk/benefit analysis of the value of the image avoid both an unsafe MRI in some patients and denial of an MRI in other patients. Specific references

and technical information from manufacturers should be consulted to determine suitability for MRI.<sup>2</sup>

The bioeffects of MRI are caused by three different types of electromagnetic radiation: (a) static magnetic field, (b) a gradient magnetic field, and (c) a radiofrequency (RF) electromagnetic field. RF may generate excessive heat in metallic components such as pacemaker leads or thermolabile catheters and melt the conductive components. RF energy can be different in magnetic fields of different strength. Implants that are safe at one field strength may not be safe at lesser or stronger field strengths. Strong magnetic fields can induce small voltages changes in blood, which is electrically conductive. The voltage changes can induce ST- and T-wave changes in the electrocardiogram reading. The physics of the interaction of strong magnetic fields, RF energy, and patients can be complex, and expert analysis by magnetic physicists may be required when safety questions arise.

Factors that make anesthesia for patients in the MRI suite different from the operating room include lack of patient accessibility for airway management, noise level, and the lack of immediately available resuscitation equipment.<sup>3</sup>

### Who will be responsible for sedating my child?

Sedation policies and personnel responsible for sedation vary greatly among institutions. The demand for sedation outside the operating room for diagnostic and interventional procedures in children has increased dramatically in the past decade. Although the risk of a serious adverse outcome from sedation is low, the incidence of timely rescue interventions is greater than 1 in 100. This requires the immediate availability of resuscitation equipment and personnel trained in respiratory management.<sup>4</sup> The goal for sedation is a cooperative and comfortable child who can maintain a patent airway with satisfactory ventilation and oxygenation. The line, however, between moderate sedation and deep sedation is not easily defined, and the likelihood of passing into a level of deep sedation is high.<sup>5</sup> Physicians responsible for sedation at different institutions include radiologists, emergency department physicians, critical care physicians, and anesthesiologists. The presence of the anesthesiologist provides an individual with expert airway management skills and someone who can quickly convert to a general anesthetic if sedation fails.

The patient's mother was assured that at this institution, all sedation for imaging procedures is supervised by a pediatric anesthesiologist with the assistance of trained nurses. All patients undergo a thorough preoperative evaluation, and a plan for sedation is developed for each child depending on his or her coexisting problems.

**TABLE 34.1** Magnetic Resonance Imaging Zones

<b>Zone I:</b>	Outside the magnetic field. Accessible to the general public
<b>Zone II:</b>	Area between freely accessible area (zone I) and controlled zones III and IV Patient and family member movement is supervised. Patient screening is usually done in zone II.
<b>Zone III:</b>	Area where injury can occur if unscreened personnel or patients can incur injuries if noncompatible ferromagnetic objects or equipment are present. Zone III must be strictly restricted.
<b>Zone IV:</b>	Magnetic resonance scanner room. This room must be clearly delineated, and a large red “Magnet On” light must be clearly visible. If cardiopulmonary resuscitation is required in zone IV, MR-trained personnel should stabilize the patient and evacuate to zone II as quickly as feasible.

### Is my baby at risk from the contrast agent?

The patient’s mother had heard about the potential risks from MRI contrast agents and asked about her infant. Nephrogenic systemic fibrosis (NSF), initially called *nephrogenic fibrosing dermopathy* has been associated with gadolinium-containing MRI contrast agents. NSF is characterized by tissue fibrosis that causes skin thickening and joint contractures. Collagen deposition can also occur in the lung, skeletal muscle, heart, diaphragm, and esophagus. Gadolinium is similar to calcium regarding molecular size and bonding and can displace calcium in a variety of human tissues. Free gadolinium ions interfere with macrophage function and cause premature cell death. Noncomplexed gadolinium is unsuitable for use in humans. Contrast agents complex gadolinium with other molecules that are generally safe for humans with a half-life of 1.3 hours in patients with normal renal function. Patients with chronic renal failure have a gadolinium half-life of 30 to 120 hours. Chronic renal failure with accompanying metabolic acidosis favors dissociation of gadolinium complexes with release of free gadolinium and deposition of gadolinium salts in muscle, skin, liver, and bone. Patients with chronic renal failure appear to be at increased risk for NSF because of decreased gadolinium excretion. Current clinical recommendations are to use alternative contrast agents in patients with chronic renal failure. If gadolinium is absolutely necessary, dialysis can markedly enhance the clearance of gadolinium.<sup>6,7</sup> The risk of NSF is negligible in patients with normal renal function.

### What are the options for sedation and anesthesia?

It was explained to the infant’s mother that there are several options (Table 34.2). There is no clear advantage to any hypnotic, and the selection of a particular technique depends on the patient’s condition and anticipated length of the procedure. Sedation with an oral hypnotic such as chloral hydrate or pentobarbital may provide satisfactory sedation for completion of the MRI. If an intravenous line can be inserted, propofol may be used. An inhalation induction with sevoflurane can be performed followed by intravenous cannulation and laryngeal mask airway insertion or tracheal intubation. The primary goals of sedation or anesthesia for children during an MRI examination are a quiescent infant and minimal risk of

cardiopulmonary complications. Sedation with oral hypnotics requires fewer invasive procedures but has a greater likelihood of unacceptable patient movement.<sup>8</sup> After a discussion with the mother, the anesthesiologist decided to sedate the infant with oral chloral hydrate.

Sedation and/or anesthesia for children undergoing diagnostic procedures requires a system that ensures proper pre-anesthesia evaluation, technique selection, airway management, monitoring, and the presence of a health care provider who can promptly and effectively manage sedation failure and cardiorespiratory complications.<sup>9,10</sup> Because there is a greater risk of adverse outcomes from procedures performed outside the operating room, careful regard for potential complications is important.<sup>11</sup>

**TABLE 34.2** Techniques for Sedation for Neuroimaging

<b>Sedation</b>
<i>Oral sedatives</i>
Chloral hydrate
Pentobarbital
Midazolam
Opioids
<i>Intravenous sedatives</i>
Propofol
Dexmedetomidine
<b>General anesthesia</b>
<i>Inhalation anesthesia</i>
Pharyngeal airway
Supraglottic airway
Tracheal intubation
<i>Total intravenous anesthesia</i>
Supraglottic airway
Tracheal intubation

Thirty minutes after the oral administration of 50 mg/kg of chloral hydrate, the infant was not adequately sedated, and an additional 50 mg/kg was given. The patient was ready for the MRI scan 15 minutes after the second dose. The child was sleeping comfortably but could be aroused. The scan, however, had to be stopped after 10 minutes because of excessive patient movement.

### What is the plan for failed sedation?

The options for managing the patient when sedation alone fails to produce a satisfactory condition for the MRI scan depend on what system has been developed at the particular institution. At some institutions, the radiologists assume responsibility for sedation protocols and implementation. If sedation fails, the patient is rescheduled for a day when an anesthesiologist is available. If the anesthesiology department operates the system, an anesthesiologist is usually immediately available to provide general anesthesia. There has been no attempt to standardize sedation/anesthesia protocols for MRI examinations. There has been a trend toward institutional development of dedicated sedation teams led by critical care physicians, emergency room physicians, or anesthesiologists.<sup>12</sup>

The infant was removed from the MRI room into an induction room in a zone II area. Because he was still well sedated, a 24-gauge intravenous catheter was inserted into a vein in the dorsum of his right hand. Anesthesia was induced with ketamine 1 mg/kg followed by rocuronium 0.6 mg/kg and positive pressure ventilation provided with 1% sevoflurane in an oxygen-air mixture. The patient's trachea was intubated with a 3.5-mm inner diameter tracheal tube. The monitors were removed, and the infant was transferred to the MRI room that was equipped with an MRI-compatible anesthesia machine. After completion of the scan, the infant was transferred to the induction room for emergence and extubation. Recovery from anesthesia was performed in a recovery area of the MRI suite (zone II).

Considerations for this particular patient include the history of prematurity and the potential effect of sedatives and anesthesia on postanesthesia ventilation and the history of cyanotic heart disease. The effects of sedatives and inhaled anesthetics on postanesthesia respiratory control are variable and difficult to predict in the individual patient. A primary concern is the effect of such drugs on airway patency and respiratory control. Airway patency during the normal awake state occurs because of a complex interaction between the central nervous system and the muscles of the upper airway. Deep sedation interferes with that system and causes airway obstruction at the base of the tongue and the glottic inlet.<sup>13</sup> Standard maneuvers to alleviate airway obstruction, such as chin lift and jaw thrust, do not always alleviate the obstruction, and positive pressure ventilation may be required.<sup>14</sup> Lack of patient accessibility in the MRI unit can delay recognition of obstruction and timely intervention. Capnography permits a rapid diagnosis of hypoventilation. After completion of the study, close monitoring for several hours would be required and overnight observation indicated if there is any concern regarding the risk of apnea. Recovery from a general anesthetic may be faster than recovery from high doses of long-acting sedatives. Children with a history of obesity, sleep apnea, or

adenotonsillar hyperplasia have an increased risk of airway obstruction during sedation. General anesthesia with a laryngeal mask airway or tracheal tube would be preferred for patients with those conditions.

The infant has been stable with respect to cardiovascular function and should tolerate sedation or general anesthesia. Inhaled sevoflurane is well tolerated if ventricular function is good (preanesthetic echocardiogram). During an inhalation induction with sevoflurane, the inspired concentration should be slowly increased and must be decreased once controlled ventilation is initiated. Controlled ventilation increases the uptake of inhaled anesthetics and may produce undesired decreases in blood pressure and heart rate.

A recovery area in the immediate vicinity of the MRI suite improves patient flow and operational efficiency. The recovery area can be staffed with recovery room nurses or nurses trained and oriented by the recovery room staff.

### KEY MESSAGES

1. In the vicinity of an MRI scanner, patients with implanted ferromagnetic objects may be at risk for injury or damage to the device from the strong magnetic field.
2. Sedation and/or anesthesia for children undergoing diagnostic procedures requires a system that ensures proper preanesthetic evaluation, technique selection, airway management, monitoring, and the presence of a health care provider that can promptly and effectively manage sedation failure and cardiorespiratory complications.
3. There has been a trend toward institutional development of dedicated sedation teams led by critical care physicians, emergency room physicians, or anesthesiologists.

### QUESTIONS

1. What is the mechanism by which nephrogenic systemic fibrosis (NSF) occurs after exposure to MRI contrast agents?

Answer: Gadolinium, the primary MRI contrast agent, is similar to calcium with respect to molecular size and bonding and can displace calcium in human tissues and cause fibrosis. Patients with renal failure are more susceptible to NSF because the elimination time for gadolinium is prolonged.

2. What mechanism causes MRI-induced interference with the electrocardiograph (ECG)?

Answer: The radiofrequency field generated by a strong magnetic field can produce small voltage changes in the blood that cause ST-T wave changes in the ECG.

3. In what zones of the magnetic resonance imaging suite is injury to patients or personnel most likely to occur?

Answer: Injury to patients and personnel can occur in zones III and IV if noncompatible ferromagnetic objects are present. Movement in these areas must be restricted and any objects screened for magnet compatibility.

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# Evidence-Based Prevention of Postoperative Nausea and Vomiting

Richard J. Pollard

## CASE FORMAT: STEP BY STEP

A 25-year-old, 5' 9", 57-kg triathlete was running on a street when she fell and injured her arm. A distal radial fracture was diagnosed in the emergency department, and an orthopaedic surgeon was consulted. The patient was scheduled for repair of the fracture in the ambulatory surgery center. Intravenous (IV) morphine (6 mg) was administered in the emergency department for analgesia. She was very anxious about the surgery and her subsequent rehabilitation.

The patient had not undergone surgery or anesthesia previously. She did not use tobacco, alcohol, illicit drugs, or nonprescribed drugs. She did have a history of significant motion sickness. Physical examination revealed a lean, athletic-appearing young woman. Her blood pressure was 90/60 mm Hg with a heart rate of 55 beats per minute.

Because the surgeon had a busy clinic and was only available in the late afternoon, the patient was fasting for more than 10 hours. She was very concerned about postoperative nausea and vomiting (PONV) because she remembered that her mother had suffered from this complication.

### What is the pathophysiology of PONV?

The underlying mechanisms that cause PONV are complex and involve both mechanical and neurologic processes. The mechanical act of vomiting requires coordination of the respiratory, gastrointestinal, and abdominal muscles. Neurologic control of the mechanical process occurs in the vomiting center located in the lateral reticular formation of the medulla oblongata. This center is in close proximity to the nucleus of the solitary tract in the brainstem and has access to the motor pathways responsible for the act of vomiting. The vomiting reflex involves the gastrointestinal tract and the chemoreceptor trigger zone (CTZ) in the area postrema. Mechanoreceptors and chemoreceptors in the lining of the gut initiate the reflex. These receptors are stimulated by contraction and distention of the gut (mechanoreceptors) or by the presence of noxious materials (chemoreceptors). Once these receptors are activated, signals are sent via the vagus nerve to activate the CTZ. The location of the CTZ in the area postrema allows the CTZ to be activated by chemical stimuli from the blood and cerebrospinal fluid. Other sites can directly affect the vomiting center via separate neurologic connections. These sites include the central nervous system (cerebral cortex, labyrinthine, vi-

sual, and vestibular apparatus) as well as the oropharynx, mediastinum, peritoneum, and genitalia.

The central nervous system has several receptors that can influence nausea and vomiting. The area postrema has large concentrations of dopamine (D<sub>2</sub>), opioid, and serotonin (5HT<sub>3</sub>) receptors. The nucleus tractus solitarius is rich in enkephalins and histaminic (H<sub>1</sub>) muscarinic and cholinergic receptors. Neurokinin-1 (NK<sub>1</sub>) receptors are found in the nucleus tractus solitarius and in the dorsal motor nucleus of the vagus nerve. Before the surgery, the patient asked the anesthesiologist the following question.

### What are my specific risk factors for PONV?

The risk factors for PONV can be categorized as: (a) patient specific, (b) anesthetic, and (c) surgical (Table 35.1). The most important patient-specific factors for PONV are female gender, young age, nonsmoker, and a previous history of PONV or motion sickness. Other patient-specific risk factors include a history of migraine headaches, anxiety, hypovolemia, and an American Society of Anesthesiologists low-risk classification.<sup>1,2</sup> Anesthetic-related risk factors include the use of volatile anesthetics, nitrous oxide (N<sub>2</sub>O), intraoperative, or postoperative opioids.<sup>3</sup> The influence of the reversal of nondepolarizing muscle relaxants with neostigmine on PONV is controversial. Earlier studies indicated that reversal with greater than 2.5 mg of neostigmine increased the incidence of PONV. A recent analysis suggests that the association between neostigmine administration and PONV is limited. Duration and type of surgery have been implicated as determinants of PONV. For every 30 minutes of surgical time, there is a predictable 60% increase in subsequent nausea. This means that a baseline risk of 10% is increased to 16% after 30 minutes of surgery and then further increased to >25% after 1 hour of surgery. For adults, there is an increased risk of PONV with intra-abdominal surgery, especially gynecologic and laparoscopic operations. Neurosurgical, ophthalmic, and ear, nose, and throat procedures are also associated with an increased risk of PONV.

Apfel et al. suggested a simplified PONV predictive score that included four factors: (a) female gender, (b) nonsmoker, (c) history of PONV or motion sickness, and (d) the need for postoperative IV opioids.<sup>4</sup> When 0, 1, 2, 3, or 4 risk factors were present, the risk of PONV was 10%, 21%, 39%, 61%, or 79% respectively. This simplified risk stratification enables clinicians to estimate the likelihood of PONV in individual patients and make appropriate adjustments in technique.

Based on Apfel's scoring system, this patient has three risk factors: female gender, non-smoker, and history of

**TABLE 35.1** Risk Factors for Postoperative Nausea and Vomiting

Patient Specific	Anesthesia Related	Surgery Related
Female	Volatile gases	Time >30 minutes
Young age	Nitrous oxide	HEENT procedures
Nonsmoker	Intravenous opioids	Major gynecological procedures
Previous PONV	Neostigmine >2.5 mg	Laparoscopy
Motion sickness	<b>Gastric suctioning</b>	
<b>Migraines</b>		
<b>Anxiety</b>		
<b>Hypovolemia</b>		
<b>Low American Society of Anesthesiologists status</b>		

Items in regular type are major risk factors. Boldface items are minor risk factors. HEENT, head ears eyes nose throat; PONV, postoperative nausea and vomiting.

motion sickness. This placed the patient's risk at 61%. The use of preoperative IV opioids, low American Society of Anesthesiologists classification, anxiety, and relative hypovolemia increased that risk.

### Do the risks of PONV in children differ from those in adults?

Eberhart et al. applied a multivariate analysis to determine the potential for PONV in children.<sup>5</sup> Risk factors for PONV in children included (a) duration of surgery greater than 30 minutes, (b) age 3 years or older, (c) strabismus surgery, and (4) a history of PONV in the patient, a sibling, or parent. When 0, 1, 2, 3, or 4 risk factors are present, the risk of PONV for the patient was 9%, 10%, 30%, 55%, or 70%, respectively.

The patient requested some form of premedicant that would decrease the likelihood of her developing PONV.

### Are there any premedicants that reduce the risk of PONV?

There are at least four receptor systems that influence PONV. Conventional wisdom in the management of patients at risk for PONV advocates the use of a technique that targets different receptor sites (Table 35.2). Multiple studies have shown the efficacy of combination versus single-agent antiemetic prophylaxis.<sup>6,7</sup> Agents used in clinical practice include 5-hydroxytryptamine (5-HT<sub>3</sub>) receptor antagonists (ondansetron, dolasetron, granisetron, and tropisetron), dexamethasone, and transdermal scopolamine.

The 5-HT<sub>3</sub> receptor antagonists are most effective when administered near the conclusion of surgery. These agents are equally effective in reducing the incidence of PONV and are all safe at recommended doses.

The corticosteroid dexamethasone has been shown to be effective as an antiemetic when given at the induction of anesthesia in doses of 4 to 5 mg. The efficacy of dexamethasone is similar to that of the 5-HT<sub>3</sub> receptor antagonists.

A transdermal scopolamine patch applied the night before surgery or 4 hours before the end of surgery can significantly reduce the incidence of PONV.<sup>8</sup> The slow onset of effect and side effects such as dry mouth and dizziness, however, may diminish the utility of scopolamine.

Although droperidol is an effective antiemetic, its use has been effectively reduced or discontinued in the United States because of the "black box" warning from the Food and Drug Administration concerning the potential risks of cardiac dysrhythmias.<sup>9</sup>

The NK<sub>1</sub> receptor antagonists, such as aprepitant, comprise the newest class of drugs purported to decrease PONV. NK<sub>1</sub> receptors are found in the areas of the brain that control the vomiting reflex, and NK<sub>1</sub> receptor antagonists may be especially effective in patients with centrally mediated PONV.<sup>10</sup>

Other drugs that have been reported to reduce the incidence of PONV, but have not been rigorously studied as yet are haloperidol, dexmedetomidine, naloxone, and nalmefene.

**TABLE 35.2** Antiemetic Drugs

<b>5-HT<sub>3</sub> Receptor Antagonists</b>	<b>Anticholinergics</b>
Ondansetron	Scopolamine
Dolasetron	<b>Antihistamines</b>
Tropisetron	Dimenhydrinate
Granisetron	<b>NK<sub>1</sub> Receptor antagonists</b>
<b>Corticosteroids</b>	Aprepitant
Dexamethasone	<b>Phenothiazines</b>
<b>Butyrophenones</b>	Promethazine
Droperidol	
Haloperidol	

A prophylactic regimen is recommended for patients at moderate to high risk for PONV. Prophylaxis is not generally recommended for low-risk PONV patients; however, because PONV is one of the largest and most costly complications after anesthesia, the anesthesiologist should consider whether the risks and cost of prophylaxis are justified for every patient. It has been shown that patients are willing to pay up to \$100 of their own money for completely effective antiemetics. An anesthesiology resident consulted with a senior colleague regarding the best anesthetic technique to prevent PONV in the patient described in this case.

### What is the best anesthetic technique to prevent PONV in this patient?

Anesthesia-related risk factors for PONV include the use of volatile inhaled anesthetics, N<sub>2</sub>O, intraoperative or postoperative IV opioids, and reversal of nondepolarizing muscle relaxants with neostigmine at doses greater than 2.5 mg. The use of regional anesthesia provides a ninefold decrease in the incidence of PONV in all populations.<sup>11</sup> If general anesthesia is required, using propofol for induction and during maintenance phases of anesthesia decreases the incidence of PONV by 19% during the first 6 postoperative hours. Propofol used in a total IV anesthesia technique reduces the risk of PONV by 25%.

Volatile inhaled anesthetics have been identified as the primary cause of PONV within the first 2 hours after surgery. The incidence of PONV when both volatile anesthetics and N<sub>2</sub>O are used may be as high as 59%.<sup>12</sup> Avoidance of N<sub>2</sub>O decreases the risk of PONV by 12%.

Whether to use IV narcotics during the perioperative period remains a quandary for anesthesiologists. On one hand, opioids reduce postoperative pain while smoothing intraoperative hemodynamic changes. On the other hand, narcotics increase the risk of PONV. Nonnarcotic analgesics such as nonsteroidal anti-inflammatory drugs and cyclo-oxygenase-2 inhibitors may have a role in reducing the need for opioids and reducing the incidence of PONV. A technique using regional anesthesia or local infiltration anesthesia in conjunction with nonnarcotic analgesics may eliminate the need for perioperative opioids.

Other preventive modalities such as supplemental oxygen or prophylactic orogastric suctioning have not been proven to reduce PONV.

The anesthesiologists agreed that the lowest-risk technique for this patient would be a regional technique such as a brachial plexus block and sedation with propofol with minimal or no opioids. Because the patient expressed a strong preference for general anesthesia, a scopolamine patch was applied at the conclusion of the preoperative interview. Dexamethasone (5 mg) was administered intravenously with the induction of anesthesia and ondansetron (4 mg) administered just before emergence from anesthesia.

Despite this aggressive prophylactic regimen, the patient experienced severe nausea on waking in the postoperative care unit.

### Is ondansetron the drug of choice in this case?

There have been very few studies regarding the treatment of patients who have failed antiemetic prophylaxis. The 5-HT<sub>3</sub> receptor antagonists have been the most frequently tested medica-

tion in rescue trials. Evidence suggests that in patients who have failed to respond to ondansetron prophylaxis, more ondansetron is no more effective than placebo. Logically, a drug that acts at a different receptor site would be a better choice.<sup>13</sup>

Several days after an otherwise uneventful recovery, the patient asked her anesthesiologist about future treatment options regarding PONV.

### In the future, are there nonpharmacological options that might be effective for this patient in the treatment of PONV?

Some nonpharmacologic treatments for PONV may be effective. Techniques such as acupuncture, acupoint stimulation, and transcutaneous nerve stimulation may have antiemetic efficacy comparable to standard treatments. There may be some resistance in clinical practice to utilization of nontraditional therapies; however, some patients are familiar with the techniques and will insist on their use. If patients request such therapy, it would be best to consult a clinician familiar with the techniques.

Although the patient's nausea resolved fully before discharge, she was concerned that the symptoms would return later.

### What can the patient expect on discharge from the surgical unit?

Nausea and vomiting occurs in one third of ambulatory surgical patients after discharge from surgery centers. Prophylactic therapy should be administered to patients susceptible to late PONV. The use of longer-acting agents in combination seems to offer the best outcome.<sup>14,15</sup>

### KEY MESSAGES

1. Anesthesia-related risk factors for PONV include the use of volatile inhaled anesthetics, N<sub>2</sub>O, IV opioids, and reversal of nondepolarizing muscle relaxants with neostigmine at doses greater than 2.5 mg.
2. When 0, 1, 2, 3, or 4 risk factors were present, the incidence of PONV in adults undergoing general anesthesia is 10%, 21%, 39%, 61%, or 79%, respectively.<sup>4</sup>
3. A prophylactic regimen is recommended for patients at moderate to high risk for PONV.

### QUESTIONS

1. What are major patient risk factors for postoperative nausea and vomiting?

Answer: Major risk factors for postoperative nausea include female gender, young age, and a history of motion sickness.

2. What receptors influence postoperative nausea and vomiting?

Answer: Dopamine, opioid, serotonin, cholinergic, and neurokinin-1 receptors influence nausea and emesis.

These receptors are concentrated in the central nervous system in the areas of the area postrema, the nucleus tractussolitarius, and the motor nucleus of the vagus nerve.

### 3. What anesthetic factors increase the likelihood of postoperative nausea?

Answer: Anesthetic factors that may increase the likelihood of postoperative nausea include the use of volatile, inhaled anesthetics and nitrous oxide, administration of postoperative opioids, and possibly the use of neostigmine to reverse neuromuscular blockade.

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# Ultrasound Guidance for Central Venous Cannulation

Bryan V. May

## CASE FORMAT: STEP BY STEP

An 81-year-old male presented with a 2-hour history of weakness and substernal chest pain caused by moderate physical activity. His medical history was significant for hypertension, chronic atrial fibrillation, multiple transient ischemic attacks, and type 2 diabetes mellitus. A 12-lead electrocardiogram revealed atrial fibrillation with an incomplete right bundle branch block, 2-mm ST depression in leads II, III, and AVF. Physical examination revealed an alert and mildly uncomfortable elderly man. The patient's vital signs were as follows: blood pressure, 164/72 mm Hg; heart rate, 92 beats per minute (irregularly irregular); and respiratory rate, 28 breaths per minute. Chest auscultation revealed no heart murmurs and faint bibasilar rales. The abdominal examination was normal. Cardiac enzymes were consistent with myocardial ischemia (elevated troponin I and creatine kinase MB levels). A transthoracic echocardiogram obtained in the emergency department revealed inferior wall akinesis and a reduced left ventricular ejection fraction (35%). Other transesophageal echocardiogram findings were concentric left ventricular hypertrophy and a small patent foramen ovale with left-to-right shunting. Carotid artery duplex ultrasound showed bilateral high-grade stenosis of both carotid arteries and a partially thrombosed left internal jugular vein. Urgent coronary artery angiography showed significant three-vessel coronary disease that was not amenable to angioplasty or stent placement. The patient was scheduled for emergent coronary artery bypass grafting.

During the brief preoperative interview, it was explained to the patient that after induction of anesthesia and tracheal intubation, a central venous catheter would be inserted into the right internal jugular vein (RIJV), and a catheter would be inserted into the pulmonary artery via the heart. The patient queried the anesthesiologist as to the need for such a catheter and potential complications.

### What are the indications for central venous cannulation?

Every year, more than 5 million central venous catheters are inserted into patients in the United States, and 200,000 are inserted into patients in the United Kingdom. Indications include

poor peripheral venous access, administration of vasoactive drugs, acute hemodialysis, rapid infusion of large volumes of resuscitation fluids, cardiac pacing, hyperalimentation, and hemodynamic monitoring.<sup>1</sup> In the perioperative period, indications are generally hemodynamic monitoring, infusion of vasoactive drugs, and fluid administration.

### What are the complications from central venous catheterization?

The potential complications from central venous cannulation are many and can be fatal (Table 36.1).<sup>2,3</sup> Chronic complications such as infection, thrombosis, or catheter fracture are related to the duration that the catheter is in place and are not common for short-term placement (such as for perioperative use). The nidus for infection, however, can be introduced during the insertion procedure, and every central venous cannulation, whether for short- or long-term placement must be managed with good sterile technique.

Complications that occur during the insertion procedure include hemorrhage (arterial or venous), hematoma formation, inadvertent carotid artery puncture, dysrhythmias, pneumothorax, catheter malposition, perforation of great vessels, pseudoaneurysm formation, arteriovenous fistula, brachial plexus injury, guidewire loss, catheter knotting, and cannulation failure. Operator experience and technique certainly influence the complication rate. Physicians with greater experience (>50 insertions) have a high success rate and a low incidence of complications. Most anesthesiologists have substantial experience with central venous cannulation at the conclusion of their training. Data from the American Society of Anesthesiologists Closed Claims Project indicated that the complications generating litigation included wire/catheter embolism, cardiac tamponade, carotid artery puncture/cannulation, hemothorax, and pneumothorax.<sup>4</sup>

Infection from a central venous catheter site is a serious and potentially lethal complication. Every effort must be made to avoid infection. Adherence to strict sterile technique during catheter insertion is essential. The use of biopatches to cover the insertion site and use of antibiotic-impregnated catheters may also reduce the infection rate; however, emergence of antibiotic-resistant bacteria is of concern. The application of antibiotic ointment to the catheter insertion site has not been shown to reduce the likelihood of infection and can promote fungal colonization of the catheter.<sup>5</sup>

The patient was transported to the operating room for coronary artery bypass grafting. He had a peripheral intra-

**TABLE 36.1** Complications of Central Venous Catheterization

Bleeding
Infection
Thrombosis
Carotid artery injury
Stroke
Hematoma formation
Pneumothorax
Hemothorax
Cardiac perforation
Cardiac tamponade
Pseudoaneurysm formation
Arteriovenous fistula
Vertebral artery injury
Dysrhythmias
Catheter fracture
Brachial plexus injury
Horner's syndrome

venous catheter and a right radial arterial line in place. After induction of general anesthesia, a transesophageal echocardiogram probe was inserted, and his right neck was positioned and prepared for central venous cannulation and insertion of a pulmonary artery catheter.

### What are the anatomic landmarks for central venous cannulation?

The three veins normally used for central venous cannulation are the internal jugular vein (right vein more frequently than the left), subclavian vein, and the femoral vein. The femoral vein is rarely chosen for hemodynamic monitoring or insertion of a pulmonary artery catheter. There is some controversy as to whether the pressure measured in the femoral vein is a true reflection of central venous pressure, and the distance from the femoral vein insertion site to the pulmonary artery exceeds the length of most pulmonary artery catheters. Femoral vein cannulation is more commonly performed in small children than in adults.

Most anesthesiologists use the RIJV as the insertion site for central venous cannulation. The RIJV has a consistent location in the carotid sheath. It is a relatively short, valveless vessel leading straight to the superior vena cava and the right atrium. Additional advantages include a decreased risk of pneumothorax, as the right lung lies more caudad than the left and avoidance of the left-sided thoracic duct. The central approach to the RIJV is very common and depends on the location of the apex of the triangle formed by the sternal and clavicular heads of the sternocleidomastoid muscle. The internal jugular vein is usually lateral or anterolateral to the carotid artery. The

carotid artery is identified, and the needle is inserted at the apex of the triangle lateral to the carotid artery and directed away from the carotid artery. If the vein is not entered, the needle can be methodically redirected more medially in small increments until the vein is found. The color of the blood can be used to differentiate venous from arterial blood, but this method is not always accurate. If it is uncertain which vessel has been cannulated, a pressure transducer can be attached to the needle or a small-bore catheter for vessel identification.

Anatomic landmarks are easily discernible in patients with well-defined anatomy. Obese patients, those with limited neck mobility, and infants do not have well-defined anatomic landmarks, and techniques dependent on anatomic identification will not be as reliable.

A 22-gauge finder needle was inserted via a central approach (apex of the two heads of the sternocleidomastoid muscle) in an attempt to locate the RIJV; multiple attempts with the finder needle were required to locate this vein. An 18-gauge, 4-inch needle attached to a 5-mL syringe was inserted in the same plane as the finder needle and advanced. Bright red blood was aspirated. After syringe removal, bright red blood pulsated from the needle. The needle was removed, and pressure was applied to the puncture site. Despite the pressure, a hematoma developed on the right side of the patient's neck. With the continued application of pressure, the hematoma stopped expanding. An ultrasound device with a 5-MHz probe was brought to the operating room. Ultrasound imaging of the right neck showed that the RIJV was lying directly on top of the carotid artery. Imaging demonstrated a hematoma surrounding and compressing the RIJV. Although the caliber of the RIJV was decreased by the hematoma, ultrasound guidance facilitated catheterization of the RIJV.

In this case, the patient's RIJV was lying directly above the carotid artery. The finder needle eventually located the RIJV, but the cannulation needle penetrated the RIJV and punctured the carotid artery. Ultrasound guidance allowed prompt identification of the RIJV leading to successful cannulation. Ultrasound imaging to facilitate central venous cannulation was first reported in the anesthesia literature in the 1970s, and many studies have shown the usefulness of ultrasound, especially for the internal jugular vein.<sup>6,7</sup> Broad acceptance by anesthesiologists has been slow to occur. In 2001, the Agency for Healthcare Research and Quality and in 2002, the National Institute for Clinical Excellence recommended ultrasound guidance for elective cannulation of the internal jugular vein in adults and children. This document has had little impact on practicing anesthesiologists. There are several practical reasons that ultrasound guidance for central venous catheter insertion has not become more prevalent. The evidence that ultrasound guidance is clearly superior to traditional anatomic techniques has not been convincing.<sup>8,9</sup> Ultrasound equipment has not been routinely available in every operating room, and delays in finding and preparing the ultrasound machine are considered unjustified if the equipment is unavailable.

### How can ultrasound guidance facilitate central venous catheterization of the RIJV?

The two commonly used techniques for ultrasound guidance are static and dynamic (real-time). The static method is relatively quick and requires no sterile preparation of the ultra-

**TABLE 36.2** Technique for Dynamic Ultrasound-Guided Central Venous Cannulation

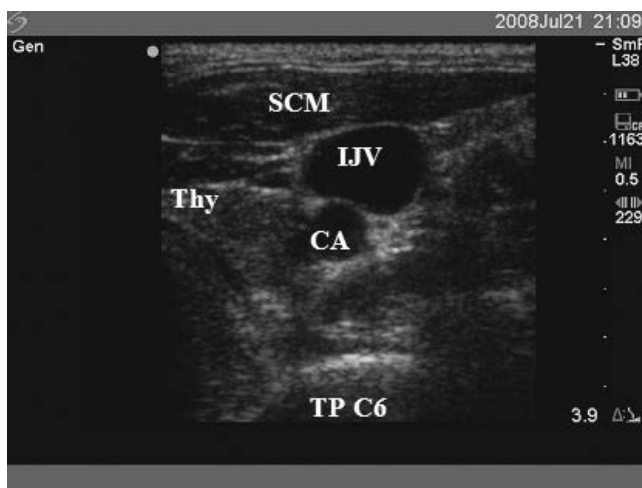
1. Position the patient's head with ultrasound guidance. The head should be rotated to maximize the distance from the carotid artery to the internal jugular vein and maximize the right internal jugular vein's diameter.
2. The cannulation site is prepped and draped in sterile fashion.
3. The ultrasound probe is inserted into a sterile sheath.
4. The internal jugular vein is identified. The jugular vein is easily compressed and should be lateral to the carotid artery, which is round and pulsatile.
5. The internal jugular vein is centered on the ultrasound screen.
6. The puncture needle is inserted at a 45-degree angle along the intercept path with the vein.
7. The accuracy of vessel puncture is determined by ultrasound, blood color, or pressure transduction.
8. The guidewire is threaded into the vein, the vein is dilated, and a catheter is threaded into the vessel.

sound probe. The operator identifies and centers the vein on the ultrasound probe. An indelible mark is placed on the skin to identify the needle insertion point, and a second mark is made distal to the first along the course of the vein. The line determined by the two points guides the operator as to the course of the vein. The probe is removed, and the patient is prepped and draped for cannulation.

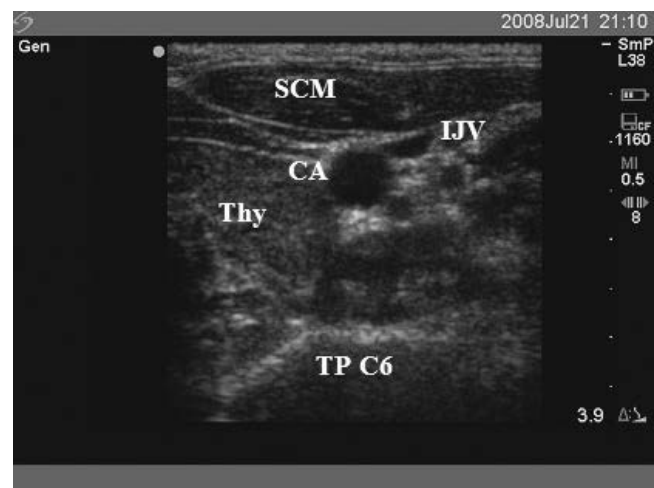
The dynamic method requires placing the probe in a sterile sheath after the patient has been prepped and draped (Table 36.2). The operator uses the probe to locate the vein, which is usually lateral to the carotid artery and is easily compressed with pressure on the probe (Figs. 36.1 and 36.2). Once identified, the vein is centered on the ultrasound screen, and the needle is inserted at a 45-degree angle toward the vein along the anticipated intercept path. The needle can be seen as

an echogenic line as it passes through tissue planes. The short axis is generally used to localize the vein and avoid the carotid artery. It may be beneficial to rotate the transducer 90° to the longitudinal plane to better identify the tip of the needle as it approaches the vessel lumen. The dynamic technique is more cumbersome than the static technique and requires practice for a lone operator. An assistant who can hold and manipulate the probe while the operator is inserting the needle can be quite helpful.

The ultrasound probe can be useful for positioning the patient's head. Head rotation can alter the relationship of the internal jugular vein to the carotid artery. Ultrasound imaging can help determine optimal rotation to maximize the distance between the carotid artery and jugular vein and can maximize the vein's diameter.



**Figure 36.1 • Axial Ultrasound Image of the Left Anterior Neck.** The internal jugular vein can be seen lateral to the carotid artery and appears patent when minimal pressure is applied to the ultrasound transducer. CA, carotid artery; IJV, internal jugular vein; Thy, thyroid gland; TP C6, transverse process of sixth cervical vertebra.



**Figure 36.2 • Axial Ultrasound Image of the Left Anterior Neck.** Application of pressure to the ultrasound transducer compresses the internal jugular vein, making identification and cannulation difficult. CA, carotid artery; IJV, internal jugular vein; Thy, thyroid gland; TP C6, transverse process of sixth cervical vertebra.

### Should ultrasound guidance for central venous cannulation be a standard of care for anesthesiologists?

Declaring a device or technique as a standard of care requires clear evidence of efficacy and ready availability of the device. The evidence to date does not demonstrate clear superiority. Part of the failure to prove that ultrasound guidance is better may be a lack of training with ultrasound guidance. The RIJV is generally easy to recognize with ultrasound, but cannulation is not always easy. The ultrasound image provides a two-dimensional image, but anatomy is three dimensional. It is not always easy to accurately determine the position of the cannulation needle with ultrasound. A standardized, formal teaching program in ultrasound guidance for central venous catheterization may improve performance to the point that a clear difference in insertion efficiency with reduced complications is evident.<sup>10</sup>

Experience is another factor that may make the case for ultrasound guidance less clear. Anesthesiologists are generally very experienced with central venous cannulation using anatomic landmark techniques, and comparative studies with anesthesiologists may be less convincing than with less-experienced practitioners. If anesthesiologists acquire ultrasound guidance skills, it may ultimately prove ultrasound to be a superior technique even in the hands of experienced practitioners.<sup>11</sup>

Ultrasound machines have become more commonplace in the operating room. Stand-alone units as well as transesophageal echocardiogram machines equipped with external probes are often readily available. The development of small high-quality ultrasound units will undoubtedly increase access for the anesthesiologist. Probe selection depends on the patient's size and the depth of the vessel. Better resolution is achieved with a high-frequency ultrasound probe. Tissue penetration, however, decreases with increasing frequency.

The preponderance of evidence suggests that ultrasound guidance will eventually be the standard of care. Anesthesiologists should become skilled with both anatomic landmark and ultrasound-guided central venous catheterization. If anatomic landmark techniques fail, ultrasound may reveal why failure occurred and may provide guidance for successful cannulation.

As anesthesiologists obtain more experience with ultrasound-guided central venous cannulation, the procedure should become more successful, safer, and more efficient.<sup>12</sup>

#### KEY MESSAGES

1. Indications for central venous line insertion include poor peripheral venous access, administration of vasoactive drugs, acute hemodialysis, rapid infusion of large volumes of resuscitation fluids, cardiac pacing, hyperalimentation, and hemodynamic monitoring.

2. At the level of the apex of the triangle formed by the sternal and clavicular heads of the sternocleidomastoid muscle, the internal jugular vein usually lays lateral or anterolateral to the carotid artery.
3. Applying gentle pressure via the ultrasound probe will compress the internal jugular vein but not the adjacent carotid artery.

#### QUESTIONS

1. What are the major complications of central venous cannulation via the internal jugular vein?

Answer: Major complications include hemorrhage, hematoma formation, stroke, perforation of major vessels, and cardiac tamponade.

2. What are the advantages of ultrasound guided cannulation of the internal jugular vein?

Answer: Ultrasound identification of the internal jugular vein is especially helpful when normal anatomic landmarks are not easily defined. Obese patients, patients with limited cervical mobility, and infants are cases where ultrasound guidance is quite helpful.

3. What is the primary way to differentiate the carotid artery from the internal jugular vein with an ultrasound probe?

Answer: The carotid artery is round, pulsatile, and relatively non-compressible. The internal jugular vein is generally irregular in shape and easily compressed with the probe.

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# Regional Anesthesia Outcomes

Justin Lane and Brian D. O'Donnell

## CASE FORMAT: STEP BY STEP

A 68-year-old man was scheduled for elective repair of an asymptomatic 6.5-cm abdominal aortic aneurysm. He had a myocardial infarction 3 years previously, resulting in endovascular stenting of his left anterior descending and circumflex coronary arteries. He remained asymptomatic of recurring anginal symptoms. The patient was a smoker with a 50 pack-year history but quit after the myocardial infarction. He returned to normal activity, lost weight, and could climb two flights of stairs without difficulty. He had no known drug allergies, and his medications were as follows: aspirin, 75 mg daily; atorvastatin, 10 mg daily; atenolol, 25 mg twice daily; and enalapril, 5 mg daily.

He had a previous uneventful general anesthetic for inguinal hernia repair 10 years ago.

On examination, the patient's vital signs were as follows: temperature, 36.5°C; blood pressure, 125/90 mm Hg; heart rate, 50 beats per minute; and respiratory rate, 16 breaths per minute. His body mass index was 28. Examination of the cardiovascular and respiratory systems was normal. Airway examination revealed Mallampati grade I with normal mouth opening and a four-finger thyromental distance. The patient's electrocardiograph reading revealed sinus rhythm with normal PR and QRS intervals but with voltage evidence of left ventricular hypertrophy (Fig. 37.1). Transthoracic echocardiography was performed and showed mild concentric left ventricular hypertrophy, structurally normal valves with trivial mitral regurgitation, and normal function with an ejection fraction calculated at 58%.

Review of the patient's blood results (Table 37.1) revealed evidence of renal impairment, prompting discontinuation of angiotensin-converting enzyme inhibitor therapy.

### How might this patient's preoperative physiological status be optimized?

The American Heart Association/American College of Cardiology 2007 revised guidelines on preoperative assessment of patients undergoing noncardiac surgery<sup>1</sup> stratify this man into a high-risk group with an expected incidence of either cardiac death or nonfatal myocardial infarction of more than 5%. With regard to reducing risk in those with known coronary artery disease, the guidelines ask four questions:

1. What is the amount of myocardium in jeopardy?
2. What is the ischemic threshold, that is, the amount of stress required to produce ischemia?

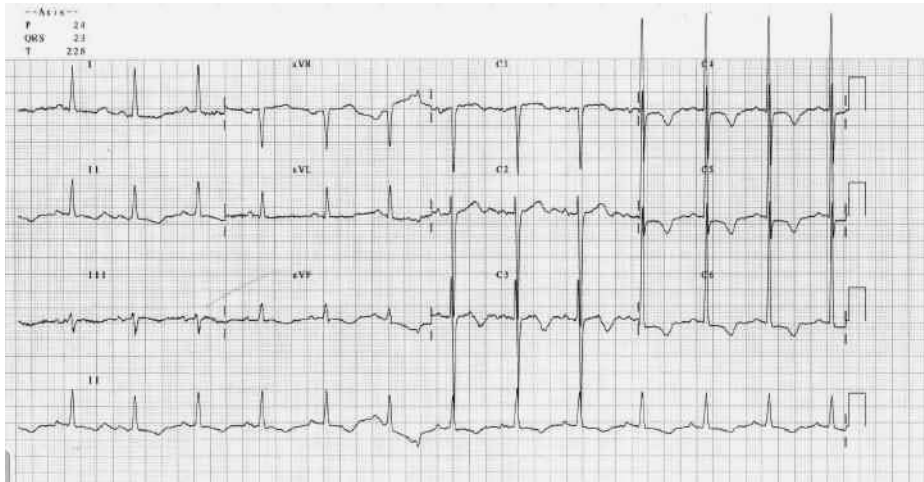
3. What is the patient's ventricular function?
4. Is the patient on his or her optimal medical regimen?

To answer these questions, the patient's clinical history holds a number of vital pieces of information: (a) he is asymptomatic regarding intercurrent ischemic heart disease; (b) he has excellent exercise tolerance; (c) he is in sinus rhythm, and his ventricular function is normal; (d) he was taking an antiplatelet agent, a  $\beta$ -blocker, an angiotensin-converting enzyme inhibitor, and a statin; and (e) his heart rate and blood pressure are well controlled. The patient received coronary artery stents to the anterior cardiac circulation, and the myocardium supplied by this area is at risk in the event of stent occlusion. However, the American Heart Association/American College of Cardiology states that "... because additional coronary restenosis is unlikely to occur more than 8 to 12 months after PCI [percutaneous coronary intervention], it is reasonable to expect ongoing protection against untoward perioperative ischemic complications..." The amount of stress that may produce ischemia is uncertain in this patient.

Therefore, whether alterations to medication and further cardiovascular evaluations are necessary must be considered. Continuing antiplatelet therapy with aspirin may contribute to additional blood loss, however, the phenomenon of late stent stenosis following antiplatelet therapy discontinuation justifies continuation in this setting.<sup>2</sup>  $\beta$ -Blockade should be continued in the perioperative period, and the patient's heart rate should be titrated to less than 65 beats per minute.<sup>1,3</sup> Favorable outcomes have been reported with the continuation of statin therapy; discontinuation of long-term statin therapy worsens perioperative cardiac outcomes.<sup>4</sup> Angiotensin-converting enzyme inhibitor therapy was discontinued in this case because of renal impairment. Finally, Polldermans et al<sup>3</sup> report that the further investigation of patients with  $\beta$ -blockade and good heart rate control is unnecessary and delays surgery. In summary, the best available evidence supports the continuation of aspirin, atenolol, and atorvastatin in this man's case, thereby permitting surgery without further cardiac assessment.

### What would be the optimal anesthetic plan for this man's open aortic aneurysm repair?

The intraoperative management of this case warrants a number of considerations including appropriate monitoring, choice of anesthesia technique, transfusion threshold, the use of coronary vasodilators, heart rate titration and analgesic technique, to name but a few. Particular attention should be paid to intra- and postoperative pain management.



**Figure 37.1** • This electrocardiogram shows evidence of left ventricular hypertrophy with the combined S wave in  $V_3$  and the R wave in aVL measuring  $>28\text{mm}$  (Cornell Criteria [Casale PN, et al. *Circulation* 1987;75: 565–572]). Also note the associated left ventricular strain pattern, manifest as T-wave inversion, most evident from  $V_3$  to  $V_6$ .

The anesthetic plan for this man included the following:

- Invasive monitoring of cardiovascular parameters
- Nitrous oxide-free general anesthesia with endobrachial intubation and positive pressure ventilation
- Epidural catheter placement at the T8 level for intra- and postoperative analgesia using a combination of local anesthetic agent (bupivacaine) and strong opiate (fentanyl)
- High-dependency unit or intensive care unit admission following surgery

### What is the rationale for this anesthetic plan?

**Monitoring** Noninvasive monitoring with an electrocardiogram,  $\text{SpO}_2$ , and noninvasive blood pressure should be employed as routine. The use of online ST-segment monitoring with electrocardiogram leads placed in either  $V_5$  and  $V_4$  configuration may facilitate the detection of intraoperative and postoperative myocardial ischemia and infarction.<sup>5</sup> Detecting intraoperative coronary ischemia may facilitate the early administration of coronary vasodilators (nitrates). However, routine use of either ST-segment monitoring or nitrates has not

been associated with improved cardiac outcomes in this patient group.<sup>1</sup> Nitrates may assist in afterload and blood pressure control following placement of the intraoperative aortic cross-clamp.

Invasive blood pressure monitoring is best used during major vascular surgery, facilitating detection of beat-to-beat variation, thus allowing rapid intervention when necessary.<sup>6</sup> The use of central venous cannulae is also recommended in this case to facilitate the administration of vasoactive medications and examine trends in central venous pressure. Pulmonary artery catheters are not routinely recommended and may contribute to patient morbidity.<sup>7</sup>

**Anesthesia Technique** General anesthesia is the preferred anesthesia modality for open repair of aortic aneurysms. There are no data describing definite benefits regarding the use of specific general anesthetic techniques or agents. Balanced anesthesia with muscle relaxation and multimodal analgesia is advocated. Of particular importance is the maintenance of normal cardiovascular parameters, especially heart rate and blood pressure. Titration of the patient's heart rate to 65 beats per minute or less with  $\beta$ -blockers has been shown to reduce the likelihood of developing cardiovascular complications in the postoperative period.<sup>3</sup>

Nitrous oxide ( $\text{N}_2\text{O}$ ) should be avoided in this case for a number of reasons. Myles et al reported an increase in major morbidity in patients undergoing laparotomy using  $\text{N}_2\text{O}$ -based anesthesia. Complications such as postoperative confusion and postoperative nausea and vomiting were also significantly increased after exposure to  $\text{N}_2\text{O}$ .<sup>19</sup>  $\text{N}_2\text{O}$  may also lead to gaseous expansion of intestinal lumen, making access to the retroperitoneum difficult for the surgeon.

**Analgesia** Effective analgesia is an essential component to balanced anesthesia. It has been described as a fundamental human right.<sup>8</sup> Pain contributes significantly to negative outcomes following surgery. Poor postoperative analgesia has been associated with higher rates of respiratory tract infection<sup>9</sup> and myocardial ischemia,<sup>10,11</sup> prolonged hospital stay, unplanned hospital admission, and increased usage of opiate analgesia.<sup>12</sup> Poor postoperative pain control has also been implicated in increased procedural cost.<sup>13</sup>

**TABLE 37.1** Preoperative Blood Results

Parameter	Result
Hemoglobin	16.2 g/dL
Platelet count	$425 \times 10^3$ per $\text{mm}^3$
White cell count	$8.7 \times 10^3$ per $\text{mm}^3$
Prothrombin time	12 seconds
Activated partial thromboplastin time	28 seconds
Sodium	148 mEq/L
Potassium	4.3 mEq/L
Urea	8.4 mmol/L
Creatinine	219 mmol/L
Glucose	5.1 mmol/L

At the physiologic level, pain results in alterations to neuroendocrine responses referred to as the *surgical stress response*. The surgical stress results in increased sympathetic activity, which in turn increases heart rate, contractility, and peripheral vascular resistance. This may lead to a reduction in myocardial oxygen supply, thereby precipitating ischemia.

Epidural analgesia provides superior analgesia compared to conventional opiate-based systemic regimens.<sup>9,14,15</sup> Epidural analgesia blunts the surgical stress response and resultant sympathetic stimulation, which may confer a cardioprotective effect. It may also produce vasodilation of epicardial blood vessels, improving myocardial blood flow and preventing myocardial ischemia.<sup>16,17</sup> An epidural catheter placed at the level corresponding to the most proximal dermatome of the surgical incision ensures reliable and predictable analgesia. Appropriate thoracic epidural catheter placement is recommended for major abdominal surgery.<sup>18</sup>

In summary, balanced anesthesia with effective epidural analgesia contributes significantly to improving patient outcome.

A 14-gauge intravenous cannula was placed in the patient's right forearm, and 1 L of Hartmann's solution was administered over 45 minutes. An epidural catheter was placed before induction of general anesthesia at the level of T8. After a negative aspiration test for blood and cerebrospinal fluid, a test dose of 2 mL 0.25% bupivacaine was administered. This dose failed to produce signs consistent with an intrathecal block at 10 minutes. Invasive arterial blood pressure was next established.

General anesthesia was induced using fentanyl (2 µg/kg), propofol (1.5 mg/kg), and vecuronium (0.1 mg/kg). The patient's airway was intubated with an 8.5-mm internal diameter cuffed endotracheal tube, and his lungs were ventilated with 50% oxygen in air to achieve normocarbia. Anesthesia was maintained with sevoflurane titrated to effect. Hemodynamic parameters (heart rate and blood pressure) were kept within 10% of the starting values. Central venous access was established after anesthesia induction. An additional 10 mL of 0.25% bupivacaine was administered into the epidural catheter at this stage.

The intraoperative course was uneventful with an aortic cross-clamp time of 40 minutes. Intravenous glyceryl trinitrate was used to control the patient's blood pressure during the cross-clamp period. Phenylephrine 100-µg bolus doses were used to control blood pressure when the aortic cross-clamp was released. The total estimated blood loss was 750 mL, resulting in a hemoglobin level of 11.2 g/dL at the end of the case. No blood products were administered. Intraoperative analgesia consisted of an epidural infusion of 0.1% bupivacaine with 2 µg/mL of fentanyl at a rate of 8 mL per hour. Intravenous paracetamol 2 g was also administered. Immediately following surgery, the sevoflurane was discontinued, neostigmine and glycopyrrolate neuromuscular block reversal were given, and the trachea was extubated. The patient was transferred to the high-dependency unit where he made an uneventful recovery over the following 48 hours.

### How should this man's pain be managed after surgery?

Epidural analgesia should be continued and titrated to effect with a continuous infusion of 0.1% bupivacaine with 2 µg/mL

of fentanyl. Adjuvants, such as paracetamol should be given around the clock (intravenously every 6 hours during the high-dependency unit stay and orally afterward). Nonsteroidal anti-inflammatory drugs should be avoided because of this patient's impaired renal function.

Pain was measured on a verbal rating scale (0–10) at rest and on movement. Zero corresponded to no pain, and 10 corresponded to the worst imaginable pain. Measurement occurred hourly for the first 24 hours and every 4 hours. The epidural infusion was titrated to keep the dynamic pain score at 3 or less at all times. The epidural catheter was removed on the third postoperative day. Removal was timed to be a minimum of 12 hours after and 4 hours before subcutaneous low-molecular-weight heparin (deep venous thrombosis prophylaxis) as per American Society of Regional Anesthesia/European Society of Regional Anesthesia consensus guideline.<sup>20</sup>

In summary, a 68-year-old man with significant comorbidities underwent major aortic surgery to repair an abdominal aortic aneurysm. Continuation of long-standing medication pre-operatively and the use of thoracic epidural analgesia facilitated the safe conduct of anesthesia, blunting the adverse effects of major vascular surgery on the myocardium.

### KEY MESSAGES

1. Pain contributes to negative postoperative outcomes following major abdominal surgery such as myocardial ischemia.
2. Epidural analgesia is superior to opiate-based systemic analgesia and attenuates the surgical stress response.
3. Thoracic epidural analgesia, particularly when maintained postoperatively, may help to prevent perioperative myocardial ischemia and infarction.

### QUESTIONS

1. What is the role of thoracic epidural analgesia in the prevention of myocardial ischemia in abdominal aortic aneurysm repair?

Answer: Pain contributes to negative postoperative outcomes following major abdominal surgery such as myocardial ischemia. Neuroendocrine responses and sympathetic activation increase myocardial oxygen demand and reduce supply. Extradural analgesia provides superior pain relief to opiate-based analgesia and attenuates the surgical neuroendocrine stress response. Thoracic epidural analgesia also dilates epicardial blood vessels improving myocardial blood flow. Thus, epidural analgesia may help prevent complications such as postoperative myocardial ischemia and infarction.

2. What are the considerations for removing an epidural catheter in a patient receiving deep vein thrombosis prophylaxis using subcutaneous low-molecular-weight heparin?



Answer: Neuraxial instrumentation in patients receiving low-molecular-weight heparin may increase the risk of extradural hematoma and resultant neurological injury. Neuraxial instrumentation (catheter removal or insertion) should be timed to be a minimum of 12 hours after and 4 hours before administering subcutaneous low-molecular-weight heparin. Published American Society of Regional Anesthesia /European Society of Regional Anesthesia consensus guidelines exist.

### 3. Why do traditional outcome measures show no difference following regional anesthesia compared with general anesthesia?

Answer: Traditional outcome measures (mortality and major morbidity) show no difference when studied across large patient populations. Although pain has not been considered a traditional outcome, the superiority of regional anesthesia techniques over systemic opioids has been consistently shown. There are proven benefits in certain situations and certain subgroups. The use of neuraxial anesthesia in patients with coronary artery disease undergoing major cardiac or vascular surgery appears beneficial and is more pronounced for thoracic than lumbar epidurals and when epidurals are used in the postoperative period.

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# Ultrasound Guidance for Peripheral Nerve Blockade

Brian D. O'Donnell

## CASE FORMAT: REFLECTION

A 95-year-old, 63-kg woman fell down a flight of stairs. She sustained a comminuted midhumeral fracture to her right arm and a Lisfranc fracture-dislocation of her right foot. Both fractures required operative management. Other than mild ecchymosis around her right eye and some tenderness in her right flank, she had suffered no other injuries.

The patient had a history of falls and sustained a hip fracture 3 years earlier, which required a hemiarthroplasty, performed under general anesthesia. At that time, she was discovered to have aortic stenosis with a gradient of 85 mm Hg across the aortic valve. No cardiothoracic surgical intervention was planned. Before her fall, she was independently mobile and self-caring, living in sheltered accommodation. Her medication consisted of aspirin 75 mg daily and metoprolol 10 mg daily. She had no known drug allergies.

On examination, the patient's vital signs were as follows: temperature, 36.5 °C; blood pressure, 155/75 mm Hg; heart rate, 52 beats per minute; and respiratory rate, 16 breaths per minute. The patient's breath sounds were vesicular. Auscultation of her precordium revealed a loud pansystolic murmur loudest at the left sternal border, radiating to the carotids. There was a palpable thrill on the anterior chest wall. Her physical examination was otherwise unremarkable.

The patient's electrocardiograph reading revealed sinus rhythm with left axis deviation and left ventricular hypertrophy (Fig. 38.1). A transthoracic echocardiogram was performed and showed concentric left ventricular hypertrophy, severe aortic stenosis, and mild mitral regurgitation. The gradient across the aortic valve was estimated to be 105 mm Hg with an estimated valve surface area of less than 0.5 cm<sup>2</sup>.

Following discussion with the patient, it was decided to proceed with both surgeries consecutively under regional anesthesia. An 18-gauge intravenous cannula was placed on the dorsum of the patient's left hand, and 1 L of Hartmann's solution was slowly administered. Routine electrocardiograph, pulse oximetry (SaO<sub>2</sub>), and noninvasive blood pressure were attached and used for hemodynamic monitoring throughout the case. A 35% oxygen mask was used to deliver supplemental oxygen.

A SonoSite Titan unit (SonoSite, Titan, Bothwell, WA) with a 7- to 10-MHz Linear 38 mm probe was used to fa-

cilitate nerve localization. A sterile transparent cover was placed over the transducer, and sterile ultrasound gel was used as an acoustic couplant. The nerve block solution consisted of equal parts 2% (20 mg/mL) lidocaine with 1:200,000 adrenaline mixed with 0.5% (5 mg/mL) bupivacaine. Clonidine was added to this solution. The final block solution contained 10 mg/mL lidocaine, 2.5 mg/mL bupivacaine, and 7.5 µg/mL clonidine. In total, 20 mL of block solution was used (200 mg lidocaine, 50 mg bupivacaine, and 150 µg clonidine).

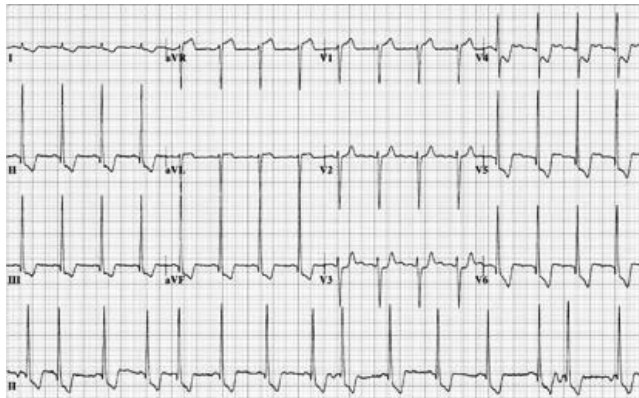
Anesthesia for the open reduction internal fixation of the foot fracture was performed using combined sciatic and femoral blocks. With the patient in a supine position, the right groin was prepared aseptically and was scanned to reveal the femoral vessels and femoral nerve. Once the femoral nerve was identified and centered in the scanning field, a Stimuplex A50 needle (B. Braun Medical, Melsungen, Germany) was introduced at the lateral edge of the scanning probe. The needle was advanced under direct vision, in long axis, toward the femoral nerve. On reaching the nerve, a test dose of 0.5 mL of block solution was injected and observed to surround the nerve, and an additional 4.5 mL of block solution was injected (Fig. 38.2).

Next, the patient's sciatic nerve was blocked at a level just proximal to the popliteal fossa. With the patient still in the supine position, the lateral thigh was prepared aseptically. Flexing the knee slightly, the ultrasound transducer was placed transversely in the popliteal fossa. The popliteal vessels, tibial, and peroneal nerves were identified. The tibial nerve was centered in the scanning field and traced proximally to visualize the site at which the sciatic nerve bifurcated. At this level, a Stimuplex A100 needle (B. Braun Medical) was inserted in the lateral thigh at the level of the scanning probe. The needle was advanced under direct vision, in long axis toward the sciatic nerve. On reaching the nerve, a test dose of 0.5 mL of block solution was injected and observed to surround the nerve. An additional 7.5 mL of block solution was injected, which facilitated complete bathing of the nerve in local anesthetic solution (Fig. 38.3).

Finally, the brachial plexus on the patient's right side was blocked using a supraclavicular approach. With the patient in a supine position, the right supraclavicular fossa was prepared aseptically. The ultrasound probe was placed in an anteroposterior orientation, and the area was scanned to reveal the supraclavicular artery, the first rib,

the pleura, and the brachial plexus. Once the brachial plexus was identified and centered in the scanning field, a Stimuplex A50 needle was introduced at the anterior edge of the scanning probe. It was then advanced under direct vision, in long axis, toward the brachial plexus. On reaching the plexus, a test dose of 0.5 mL of block solution was injected and observed to fill the brachial plexus sheath. An additional 6.5 mL of block solution was injected (Fig. 38.4).

Motor and sensory block was tested in the distribution of the brachial plexus, femoral, and sciatic nerves. Once satisfactory anesthesia had been achieved, sedation was provided using 2 mg midazolam. Surgery proceeded uneventfully, taking 4.5 hours in total. During the surgery, the patient received 2 L of Hartmann’s solution, 1.5 g cefuroxime, and 2 g intravenous paracetamol. At the end of surgery, she fulfilled the recovery room bypass criteria and was discharged pain free from the operating room to the ward. Postoperative pain was managed with a combination of oral oxycodone and paracetamol. The patient made an uneventful recovery from anesthesia and surgery and was discharged to convalescent care on the fifth postoperative day.



**Figure 38.1 • Twelve-lead electrocardiograph showing features of left ventricular hypertrophy.** Voltage criteria for LVH include:

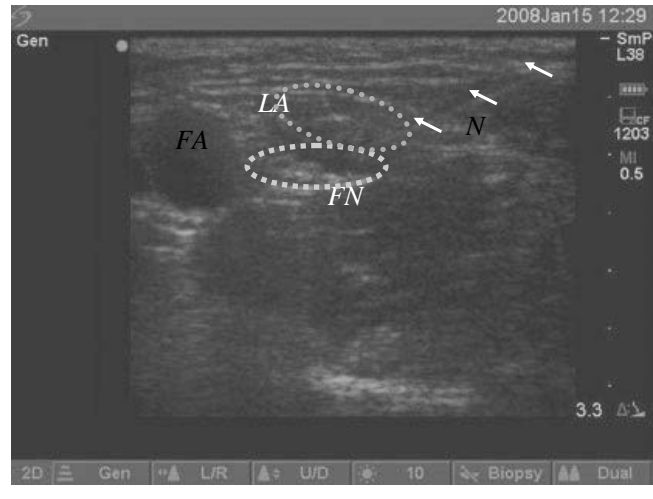
Limb leads

- R wave in lead I plus S wave in lead III >25 mm
- R wave in lead aVL >11 mm
- R wave in lead aVF >20 mm
- S wave in lead aVR >14 mm

Precordial leads

- R wave in leads V4, V5, or V6 >26 mm
- R wave in leads V5 or 6 plus S wave in lead V1 >35 mm
- Largest R wave plus largest S wave in precordial leads >45 mm

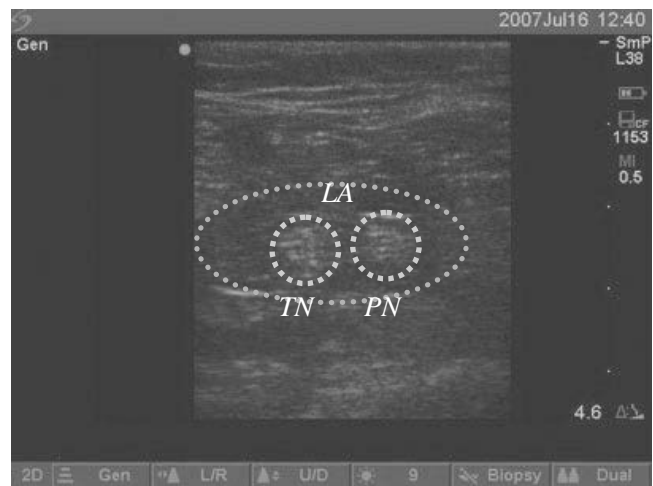
(Reproduced with permission from Edhouse J, Thakur RK, Khalil JM. ABC of clinical electrocardiography conditions affecting the left side of the heart. *BMJ* 2002;324:1264–1267.)



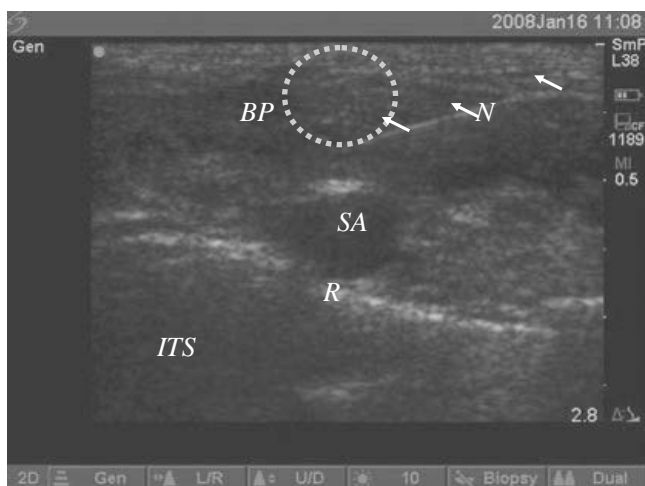
**Figure 38.2 • Ultrasound-Guided Femoral Nerve Block.** The image shows the performance of a femoral nerve block with needle visible in the long axis of the ultrasound beam. FN, femoral nerve; FA, femoral artery; N, needle; LA, local anesthetic (test dose, 0.5 mL).

**Why choose a peripheral nerve block?**

*Improved Outcome?* Outcome studies have not shown improved morbidity and mortality rates with the use of peripheral nerve blocks. Studies to date have been underpowered to detect such rare occurrences as perioperative death. Outcomes such as pain, nausea and vomiting, ambulation, and time to hospital discharge, however, have all been improved with the use of peripheral nerve block in many clinical contexts.<sup>1–3</sup> Brachial plexus blocks have been associated with improved pain outcomes following upper limb surgery.<sup>4–6</sup> A combination of



**Figure 38.3 • Ultrasound-Guided Sciatic Nerve Block.** Image showing the two parts (tibial and common peroneal) of the sciatic nerve in the proximal popliteal fossa surrounded by local anesthetic. TN, tibial nerve; PN, common peroneal nerve; LA, local anesthetic.



**Figure 38.4 • Ultrasound-Guided Supraclavicular Brachial Plexus Block.** Image showing the performance of a supraclavicular brachial plexus block, with needle visible in the long axis of the ultrasound beam. SA, subclavian artery; R, first rib; BP, brachial plexus (resembles a bunch of grapes); N, needle; ITS, intra-thoracic space.

peripheral nerve blocks facilitated excellent anesthesia and postoperative analgesia in this case.

**Reduced Physiologic Insult?** General anesthesia agents cause significant cardiac depression, vasodilatation, and hemodynamic derangement.<sup>7</sup> Although these physiologic changes are normally well tolerated in health, this patient had severe aortic stenosis, which predisposes to anesthesia-related cardiovascular morbidity and mortality.

General anesthesia also alters respiratory mechanics, resulting in lung atelectasis and intrapulmonary shunt, thereby predisposing the patient to postoperative complications such as hypoxemia and pneumonia.<sup>8</sup> Regional anesthesia permits targeted anesthesia of surgical site and facilitates surgery in awake or lightly sedated, cooperative patients. The unwanted aforementioned physiologic derangements were avoided in this case.

**Lower Level Monitoring Required?** Monitoring for this surgery under general anesthesia would have necessitated the placement of invasive arterial and central venous cannulae.<sup>9</sup> Vasopressor support, to correct predictable hemodynamic derangement accompanying general anesthesia, may have been required. Effective peripheral nerve block obviated the need to use general anesthesia in this case.

### Why use a mixture of lidocaine, bupivacaine and clonidine?

The physicochemical properties of lidocaine and bupivacaine are summarized in Table 38.1.<sup>10</sup> Lidocaine with a pKa of 7.7 has a rapid onset of action. Bupivacaine, with 98% protein binding, will provide an extended block well into the postoperative

**TABLE 38.1** Physicochemical Properties of Local Anesthetics

	pKa	Protein Binding (%)	Lipid Solubility
Lidocaine	7.8	65	366
Bupivacaine	8.1	96	3460

period. Clonidine has been shown to prolong brachial plexus blocks when administered into the perineural space.<sup>11,12</sup>

### Why ultrasound guidance?

**Block Success Rates?** Poor success rates have hampered the use and development of peripheral nerve block techniques. Blind techniques rely on imprecise end points such as paraesthesia or motor response to nerve stimulation. Ultrasound guidance facilitates placing the block needle directly adjacent to the target nerve, allowing visualization of needle, nerve, and injectate. Needle reposition is facilitated, ensuring circumferential spread of injectate around the nerve. Ultrasound guidance has been shown to increase the likelihood of a successful block (from 80% to 95%) when compared with nerve stimulation for three-in-one blocks.<sup>13,14</sup> The only study evaluating brachial plexus block techniques suggests equivalence between ultrasound and nerve stimulation.<sup>15</sup> Currently, comparative studies have not been performed with sciatic nerve block.

**Onset Time?** Not only have poor success rates hampered peripheral nerve block development, slow block onset times similarly make peripheral nerve blocks a less attractive anesthetic option. When compared with general anesthesia, peripheral nerve blocks have been shown to take on average 11 minutes longer to provide effective anesthesia.<sup>16</sup> Ultrasound guidance permits deposition of a local anesthetic agent directly adjacent to the nerve structure. The physicochemical properties of local anesthetic agents (pKa, lipid solubility) and the relative concentration of the drug (2% vs. 0.25%) largely determine block onset times. Also, the closer the solution is deposited to the nerve, the faster the agent will work. Therefore, greater precision in injectate placement as seen with ultrasound guidance, has resulted in a reduction in block onset time.<sup>15,17</sup>

**Reduction in Dose?** The dose of the local anesthetic agent used to perform peripheral nerve blocks has been greatly reduced when compared with traditional techniques. Marhofer et al<sup>14</sup> demonstrated a reduction in dose when ultrasound was compared with nerve stimulation for three-in-one block. Casati et al<sup>18</sup> estimated the ED-50 of 0.5% ropivacaine for femoral nerve block to be 15 mL under ultrasound guidance and 26 mL for nerve stimulation. Willschke et al<sup>19</sup> used as little as 0.075 mL/kg for ilioinguinal/iliohypogastric blocks in children. Clinical experience, as illustrated in this case, suggests the potential to dramatically reduce the dose of the agent required to produce successful peripheral nerve block. However,

the optimal dose of local anesthetic agent for brachial plexus and sciatic blocks has not yet been defined.

In summary, ultrasound guidance permitted the safe and effective conduct of regional anesthesia in a patient with upper and lower limb fractures, for whom general anesthesia carried significant risks. Improved block success rates and reduced onset times as seen with ultrasound guidance provided the confidence to proceed using regional anesthesia alone. In this case, ultrasound guidance permitted same-day treatment of both upper and lower limb fractures, which may not have been possible with other nerve localization techniques because of dose limitations.

### KEY MESSAGES

In experienced hands, ultrasound guidance

1. Permits precise nerve localization and perineural local anesthetic deposition.
2. Facilitates a reduction in local anesthetic dose.
3. Improves the success rates of nerve block techniques.
4. Speeds the onset time of peripheral nerve block.

### QUESTIONS

1. Does ultrasound guidance facilitate reducing the dose of local anesthetic agent needed to perform successful neural blockade.

Answer: Yes. Ultrasound guidance permits precise perineural needle and injectate placement. Visualization of circumferential perineural spread is accepted as the end point for ultrasound-guided peripheral nerve block. This permits neural blockade with very small volumes of local anesthetic agent (Riazi S, Carmichael N, Awad I, et al. Effect of local anaesthetic volume (20 vs 5 ml) on the efficacy and respiratory consequences of ultrasound-guided interscalene brachial plexus block. *Br J Anaesth* 2008;101:549–556).

2. Does ultrasound guidance make the practice of regional anesthesia under deep sedation or general anesthesia safe?

Answer: No, occult intraneural injection or intraneural catheter placement resulting in nerve injury is still possible. Conscious patients may report pain or dysesthesia should this occur. Deep sedation and general anesthesia will abolish this feedback. Real-time ultrasound guidance may detect needle tip position, but it may not prevent an operator-dependent phenomenon such as intraneural injection. It is best practice to perform regional anesthesia in conscious patients.

3. Does ultrasound guidance improve the safety of regional anesthetic techniques?

Answer: The term safety implies clinical efficacy without adverse event or harm. There is no conclusive evidence

demonstrating an improvement in patient safety with the use of ultrasound guidance for regional anesthesia. In expert hands, ultrasound guidance reduces local anesthetic dose, speeds block onset and facilitates avoidance of important related structures (arteries and veins). It may appear logical that these conditions confer a greater level of safety than blind techniques. This has not been borne out by prospective data as of yet.

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# Continuous Ambulatory Regional Anesthesia

Jason Van der Velde

## CASE FORMAT: REFLECTION

A 56-year-old woman was scheduled for an elective arthroscopic shoulder rotator cuff repair and subacromial decompression. She was a well-controlled asthmatic, on regular budesonide 200 µg through a metered dose inhaler who had never required hospital admission for her asthma.

In the preoperative assessment clinic, a continuous ambulatory regional anesthetic technique was recommended to the patient for optimal pain management. Specific informed consent was obtained for perineural interscalene catheter placement prior to general anaesthesia after discussing the risks, benefits, alternatives, and management of potential complications. Motor and sensory examination of her shoulder was performed at this clinic appointment.

On the day of surgery, the catheter was placed in the anesthetic room with standard monitoring and intravenous (IV) access. Real-time ultrasound was used for guidance throughout the procedure, which was conducted under standard aseptic conditions consisting of sterile skin preparation and draping of both patient and equipment.

After infiltration of skin and subcutaneous tissue with a local anesthetic, an 18-gauge thin-walled needle was inserted into the interscalene space between the anterior and the middle scalene muscle. Preservative-free bupivacaine (0.5% 20 mL) with 1:200,000 epinephrine was injected. A 20-gauge polyamide catheter was inserted through the needle to a depth of 3 cm beyond the needle tip. The catheter was secured with a clear adhesive dressing. The patient was noted to have both a dense motor and sensory block 30 minutes later.

General anesthesia was then induced with fentanyl 100 µg and propofol 150 mg. Anesthesia maintenance was achieved with sevoflurane and a 50:50 oxygen:air mix through a laryngeal mask airway. An uneventful 2-hour procedure followed under general anesthesia without catheter infusion. Paracetamol 1g was administered intravenously during the procedure.

The patient was pain free in the postanesthesia recovery area. Having confirmed the correct position of the perineural catheter with a thoracic inlet radiograph, a disposable elastomeric infusion pump was attached and set to infuse plain preservative-free 0.25% bupivacaine at 5 mL per hour.

On conclusion of the day's operating list, the anesthetist visited the patient on the ward. Instructions initially given

during the preoperative clinic were reiterated to both the patient and her husband. These instructions were reinforced with a patient information leaflet. The leaflet explained how to use the catheter, cautioned the patient to care for the insensate arm, and described the possible drainage that could occur. In addition, the sheet mentioned side effects including a sagging eyelid, smaller pupil, slight redness of the eye, and a possible decrease in deep breathing especially while lying down. The day and time when the catheter should be removed were written on the sheet. The patient was discharged home that evening, in care of her husband, with the contact numbers of the orthopaedic admissions ward, the district nurse team, and a letter for her general practitioner.

The patient awoke at home at 3:00 AM with pain in the lateral deltoid only. Her husband telephoned the ward, and an immediate admission was initiated. On arrival, the patient's pain scores were found to be 7/10, and rescue pain relief (intramuscular morphine) was prescribed as required. The perineural infusion was maintained for an additional 48 hours, as it continued to provide excellent pain relief to all other aspects of her shoulder. The patient was discharged home on minor analgesics thereafter, and her outpatient rehabilitation and recovery continued uneventfully.

## CASE DISCUSSION

Although greatly improving patients' long-term quality of life, shoulder procedures can be extremely painful. Immediate postoperative pain is costly, particularly in terms of length of hospital stay and rehabilitation time. With the number of procedures predicted to increase as the population ages, novel approaches to pain management are constantly being sought.

### Anesthetic and Analgesic Options

Pain is greatly exacerbated in the rehabilitation phase of treatment, particularly during physiotherapy. This pain has been shown to have a direct bearing on the functional outcome of the procedure.<sup>1</sup> Current postoperative analgesic regimens should ideally include a multimodal prescription of oral minor analgesics combined with rescue opioids.

In this particular patient, it is unclear whether this avenue has been fully explored prior to her initial discharge home. It appears that she had a single dose of IV paracetamol intraoperatively, and no nonsteroidal anti-inflammatory drugs

**TABLE 39.1** Comparison of Local Anesthetics

		<b>Lidocaine</b>	<b>Bupivacaine</b>	<b>Levobupivacaine</b>	<b>Ropivacaine</b>
<b>Block duration (min)</b>	Plain	60–120	180–360	180–360	140–200
	With epinephrine	90–180	300–480		160–220
<b>Onset</b>		Rapid	Slow	Slow	Moderate
<b>Sensory block</b>		Dense	Dense	Dense	Dense
<b>Motor block</b>		Moderate	Dense	Dense	Moderate
<b>Safety</b>		Moderately cardiotoxic	Highly cardiotoxic	Improved safety over bupivacaine	Favorable safety profile compared to bupivacaines, with less diaphragmatic impairment

(NSAIDs) were given, possibly because of exaggerated anxiety that this may worsen her asthma. Aspirin and NSAIDs may cause bronchoconstriction in approximately 10% of asthmatic patients, although they also relieve it in approximately 0.3% of patients.<sup>10</sup> As the primary mechanism is believed to be inhibition of the cyclooxygenase 1 (COX-1) enzyme, patients with aspirin sensitivity often display cross-reactions to nonselective NSAIDs that inhibit the COX-1 enzyme.<sup>11</sup> Because acetaminophen is a weak inhibitor of the COX-1 enzyme, patients with aspirin-induced asthma should not take more than 1000 mg in a single dose, but COX-2 selective NSAIDs appear to be safe in this patient population.<sup>11</sup>

Regional anesthesia is the cornerstone of multimodal analgesic regimens. Single-shot plexus blocks were first used to reduce the amount of systemic opioids administered perioperatively. The interscalene brachial plexus block provides analgesia that is superior to morphine in shoulder arthroplasty.<sup>2</sup> The advantages of a single-shot nerve block may be extended using perineural local anesthetic infusions. They have the additional benefit of expediting and improving functional recovery. The safety and efficacy of various continuous regional anesthesia techniques using portable infusions or patient-controlled boluses of local anesthetic agents through indwelling perineural catheters has been demonstrated.<sup>3</sup>

Interscalene brachial plexus blockade may be combined with a general anesthetic or used as the primary anesthetic technique for shoulder arthroscopy. Regional anesthesia for shoulder arthroscopy has been shown to require significantly less nonsurgical intraoperative time ( $53 \pm 12$  vs.  $62 \pm 13$  minutes,  $p = .0001$ ) and also decreased post-anesthesia care unit stay ( $72 \pm 24$  vs.  $102 \pm 40$  minutes,  $p = .0001$ ) compared with general anesthesia.<sup>4</sup> Administration of regional anesthesia resulted in significantly fewer unplanned admissions for severe pain management, sedation, or nausea/vomiting than general anesthesia and was accompanied by a failure rate of 8.7%. The increasing use of ultrasound to guide perineural catheter placement may lead to improved success rates.

Pain management during the transition from a dense surgical block to an analgesic block is a challenge. This may occur

when using a dilute local anesthetic solution. If a long-acting local anesthetic agent is used to establish the block, as in the case presented (Table 39.1), at about 16 hours postinsertion, gaps may become evident as patchy pain. These gaps may occur in the early hours of the morning, when staffing levels are low or when an ambulatory patient is at home. It is therefore preferable to establish blocks with a short-to-medium acting agent such as 1% prilocaine, lidocaine, or mepivacaine. If there is an area not covered by the infusion, this will become evident a few hours post procedure, thus facilitating an early alternative analgesic strategy.<sup>9</sup>

## Patient Selection Weighed Against Potential Complications

Shoulder arthroscopy and arthroplasty are performed in many centers as ambulatory procedures using continuous ambulatory regional anesthesia techniques to control postoperative pain.<sup>5</sup> Patient satisfaction is high,<sup>6</sup> the technique has reduced oral opioid requirements and sleep disturbances while improving range of motion.

Although regional anesthetic techniques provide site-specific analgesia with minor, if any, systemic side effects,<sup>7</sup> it is important to remember that whereas the technique itself does not always require inpatient supervision, the patients' premonitory condition may. Patients must be able to manage at home with the risks posed by an insensate limb. Appropriate patient selection weighed against potential complication risks, education, and follow-up are crucial when prescribing outpatient infusions.

Regional anesthesia is not associated with a greater incidence of neurologic complications than general anesthesia. The American Society of Anesthesiologists closed-claims studies suggest that the majority of reported neurological complications are actually associated with general anesthesia and incorrect patient positioning.

Complications such as hematoma formation, hoarseness, and Horner's syndrome have been reported. These issues are attributed to needle misplacement or local anesthetic either spreading to upper cervical nerve roots (C<sub>3</sub>, C<sub>4</sub>) or anteriorly to block the phrenic nerve in front of the anterior scalene muscle.



All patients should be counseled regarding the high incidence of varying degrees of ipsilateral diaphragm paralysis. This occurs subclinically in most patients and is rarely an issue unless there is a significant cardiac or respiratory comorbidity. Moderate or severe functional limitation or a baseline room-air oxygen saturation of less than 96% is not necessarily a contraindication for regional anesthesia, but inpatient supervision should be mandated to manage any potential pulmonary complications.

More serious side effects of regional anesthesia include vasovagal attacks, pneumothoraces, total spinal anesthesia, high epidural block, and inadvertent intravascular injection. The latter are very rare and will usually present perioperatively, allowing immediate management.

If ambulatory catheter dislocation or pump malfunction occurs, particularly early on during ambulatory regional anesthesia, patients are at high risk of experiencing severe surgical pain and are usually unresponsive to oral opioids and require hospital re-admission. Patients should therefore not be discharged home if they will be alone and need to be counseled to take prompt actions if block failure occurs. Patients should also be made aware of early signs of systemic local anesthetic toxicity and should be able to demonstrate clearly how to disconnect the infusion pump and access urgent medical help if this occurs.

## Infusion Considerations

Three interscalene catheter infusion strategies have been compared:<sup>8</sup> continuous infusion alone, basal infusion with patient-administered boluses, and patient-controlled boluses alone. A basal infusion of 5 mL/h of bupivacaine 0.125% combined with patient-controlled analgesia boluses (2.5 mL/30 min) proved to be the most appropriate technique.

Electronic pumps, although costly, are useful for accurate quantification of the agent infused. They are an ideal delivery option for in-hospital use. On the other hand, elastomeric disposable pumps appear to be more reliable because of simplicity.<sup>9</sup> They are essentially high-flow resistance devices and therefore are inherently safer in preventing inadvertent boluses of large amounts of local anesthetic. They are ideal for ambulatory home use because they are less bulky than electronic pumps.

There are logistical and financial advantages to undertaking shoulder surgery in an ambulatory setting; however, the approach is limited by postoperative pain being inadequately controlled by oral medication alone. Additional continuous ambulatory regional anesthesia appears to meet the challenge of providing a reliable extension of postoperative analgesia following painful surgery.

### KEY MESSAGES

1. Regional anesthesia is the cornerstone of multimodal analgesia following painful surgery. Its benefits could be extended beyond hospital stay by continuous ambulatory perineural infusions.
2. Continuous ambulatory regional anesthesia decreases length of hospital stay by providing analgesia that permits greater passive limb mobility and the avoidance of IV opioids. Patient selection and counseling is paramount.

## QUESTIONS

1. Is a long-acting local anesthetic agent ideal for establishing the initial block before starting a continuous ambulatory infusion?

Answer: No. It is preferable to establish blocks with a short-to-medium acting agent to diagnose and manage inadequate or patchy analgesia before a patient's discharge.

2. What steps can be taken to avoid inadvertent intravascular injection of local anesthetic?

Answer: Inadvertent intravascular injection of local anesthetic is best avoided by maintaining verbal contact with the patient, frequent aspirations, looking for disappearance of motor twitch after injection of the first mL of local anesthetic solution (or tissue expansion with visualization of the needle tip with ultrasound guidance), and using an adrenalin-containing test solution to evaluate and re-evaluate a perineural catheter.

3. What is the management of inadvertent intravascular injection of bupivacaine resulting in systemic toxicity?

Answer: The cornerstone of bupivacaine systemic toxicity is a 1.5mL/kg bolus of intralipid 20% over 1 minute followed by an infusion at 0.25mL/kg/min over 20 minutes whilst continuing all necessary cardiopulmonary resuscitative efforts. Repeating boluses at 5 minute intervals thereafter or increasing the rate of infusion to 0.5mL/kg/min until a stable circulation is restored may be considered.

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# Postoperative Analgesia in a Trauma Patient With Opioid Addiction

Brian D. O'Donnell

## CASE FORMAT: STEP BY STEP

A 19-year-old male was brought to the emergency department by ambulance following a motor vehicle accident. He was a restrained rear seat passenger who suffered an open fracture to his right femur after retropulsion of the driver's seat onto his knee. He had no other injuries.

On examination, the patient's vital signs were as follows: heart rate, 110 beats per minute; blood pressure, 105/65 mm Hg; respiratory rate, 24 breaths per minute; temperature, 35.5°C; and SaO<sub>2</sub>, 98% on room air. Primary and secondary trauma surveys revealed an open midshaft of femur fracture with bone protruding through a wound on the anterior thigh. The wound was soiled with particulate matter from the crash site. The patient's Glasgow Coma Scale score was 15, there were no external signs of head injury, and he had no memory loss. He was extremely agitated and complaining of severe pain. Trauma radiology included a lateral cervical spine, chest, and pelvic radiographs (all of which showed normal results). His hemoglobin level was 11.4 g/dL, and coagulation as well as biochemistry parameters were normal.

Of note, this young man was a heroin user. He had smoked heroin for 3 years and had recently begun injecting because of diminished drug effect. The absolute quantity of heroin use could not be determined. The patient had never been on a treatment program, and his last "fix" was 4 hours before the accident.

In the emergency room, a 14-gauge intravenous (IV) cannula was placed, and the patient received 2 liters of Hartmann's solution. Pain was managed with 25 mg IV morphine sulphate with little effect. The patient received 1.5 g cefuroxime, 500 mg metronidazole, and a tetanus inoculation. He was scheduled for emergency surgery, and the operating room was alerted and made ready for his arrival.

On initial preoperative assessment in the emergency room, the patient was very agitated and complaining of severe pain.

### How might the patient's pain and agitation be managed before surgery?

Acute pain after trauma originates from nociceptors at the site of injury.<sup>1</sup> Nociceptor activation results in a pain signal being conveyed along sensory fibers in peripheral nerves to the spinal cord and via a variety of pathways to several areas within the

brain. The femoral nerve is the peripheral nerve that supplies sensation to the femur.<sup>2</sup> This patient had received 25 mg IV morphine without analgesic benefit. His recent conversion from smoked to IV heroin use suggests tolerance to opiates. Tolerance to opiates is defined as a right-shift in the dose response curve, resulting in higher drug doses needed to produce the desired effect.<sup>3</sup> In patients taking long-term opiates, adequate analgesia is difficult to achieve.<sup>4</sup> Agitation in this setting may be as a result of pain. Keep in mind that agitation may be caused by injuries such as head trauma, hypoxia from pneumothorax, or hypovolemic shock resulting from blood loss. Agitation may also be caused by opiate withdrawal. Because this patient had a recent "fix," and primary and secondary surveys had ruled out head, chest injury, and hemorrhagic injury, it was assumed that pain was the primary cause of agitation. The presence of an occult injury causing agitation was considered at all times. Peripheral nerve block is one appropriate analgesic option in these circumstances.

Following a thorough preoperative assessment, the attending anesthesiologist decided to manage pain in the emergency room using a femoral nerve block.

The procedural aspects of the femoral nerve block were explained to the patient, who provided verbal consent for the block. He agreed to cooperate and remain still during the block. Electrocardiogram, noninvasive blood pressure, and SaO<sub>2</sub> monitors were attached. The open fracture was covered with a sterile surgical drape, and the patient's groin was prepared aseptically. A Sonosite Titan unit (SonoSite, Titan, Bothell, WA) with a linear 38-mm 7- to 10-MHz probe was used to guide block placement. A sterile transparent cover was placed over the ultrasound probe, and sterile ultrasound jelly was used as an acoustic couplant. The patient's groin was scanned to reveal the femoral vessels and femoral nerve. A Stimuplex A50 needle (B. Braun Medical, Melsungen, Germany) was advanced under direct vision in long axis toward the femoral nerve (Fig. 40.1). Once the needle reached the desired perineural space, 0.5 mL of 2% lidocaine with 1:200,000 adrenaline was injected after careful aspiration. The solution was observed to surround the nerve. An additional 9.5 mL of 2% lidocaine with 1:200,000 adrenaline was then slowly injected (Fig. 40.2). Over the next 10 minutes, the patient's pain improved, and his level of agitation lessened.

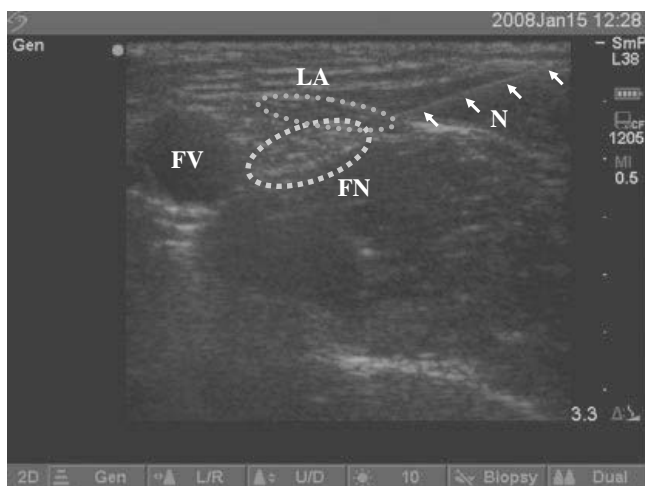
Approximately 90 minutes later, the patient was moved to the operating room where surgical toilet of the wound and intramedullary nailing of the femur fracture was planned. Although lucid and cooperative, the patient was anxious and requested general anesthesia, as he did not want to be awake during surgery.



**Figure 40.1 • Image Showing the Femoral Artery, Vein, and Nerve with the Use of Directional Color-flow Doppler.** FA, femoral artery; FN, femoral nerve; FV, femoral vein.

### How should anesthesia be provided for this man?

Both general and spinal anesthesia were considered. Spinal anesthesia would facilitate rapid and effective anesthesia. However, the combination of vasodilation associated with spinal anesthesia and relative hypovolemia from the femur fracture may have precipitated dramatic hemodynamic instability. Spinal anesthesia would necessitate turning the patient into the lateral position to gain access to the central neuraxis. This maneuver would have been technically difficult because of the patient's open femur fracture. In view of the patient's



**Figure 40.2 • Image Showing a Femoral Nerve Block being Performed with the Block Needle Visualized along the Long Axis of the Ultrasound Beam.** FA, femoral artery; FN, femoral nerve; LA, 0.5-mL test dose local anesthetic; N, needle with arrows depicting needle path.

preference and these factors, the anesthesiologist decided to proceed with general anesthesia.

The patient was considered to have a full stomach, as he had suffered a painful traumatic injury and had received opiate analgesics, both known to predispose to impaired gastric emptying.<sup>5</sup> Routine monitoring (electrocardiogram, noninvasive blood pressure, SaO<sub>2</sub>) was attached to the patient, and a second 16-gauge IV line was placed. General anesthesia was induced using a rapid sequence technique with propofol, suxamethonium, and the Sellick maneuver. The patient's airway was managed with an 8.5-mm cuffed endotracheal tube secured at 23 cm at the incisors. Anesthesia was maintained with 50% oxygen in air and 3% sevoflurane. Intraoperative analgesia consisted of 2 g IV paracetamol and 75 mg IV diclofenac sodium. The surgery took 3 hours to complete. During this time, an additional 4 liters of Hartmann's solution was administered. No blood products were administered, and the patient remained hemodynamically stable throughout the procedure. His hemoglobin level was 9.1 g/dL at the end of surgery.

On emergence in the recovery room, the patient complained of mild pain in his leg and could demonstrate return of femoral nerve motor function by flexing his quadriceps muscles. Over the next 30 minutes, his pain increased.

### How might pain be managed in the postoperative setting?

Multimodal analgesia involves the administration of two or more analgesic agents that have a different mechanism of action.<sup>6</sup> The American Society of Anesthesiologists Task Force on Acute Pain Management advocates the use of multimodal analgesia for the management of acute pain.<sup>7</sup> Multimodal analgesic regimens have been shown to provide superior analgesia compared with single agents.<sup>8,9</sup> Nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol are standard components to multimodal analgesia. Opiates administered enterally or parenterally are used in combination with paracetamol and NSAIDs for the treatment of severe pain. Because of this patient's tolerance to opioid medications, effective analgesia would be difficult to achieve with an opiate-based analgesia regimen.

A continuous femoral nerve block would provide excellent analgesia in this setting. Femoral catheters have been used successfully to provide analgesia following femur fracture in non-opioid-dependent patients.<sup>10,11</sup> As the initial femoral nerve block had worn off, it was safe to proceed with inserting a femoral catheter. Placing a catheter under anesthesia (general or regional) is a controversial matter. It might be argued that the advent of ultrasound guidance minimizes the risk of inadvertent intraneural needle or catheter placement. However, it is accepted that an awake patient, reporting dysesthesia or pain during a nerve block procedure, is an early warning of intra-neural injection. Therefore, peripheral nerve blocks are probably best placed in patients who can report symptoms of intraneural injection.<sup>12</sup> Pain on intraneural injection has been disputed as a reliable indicator of intraneural injection.<sup>13</sup> In this case, however, it was judged prudent to allow the initial rescue block to wear off before placing the perineural catheter.

The patient's right groin was fully prepared aseptically under sterile conditions. A hernia towel covered the groin and facilitated access to the expected puncture site. The ultrasound probe was covered with a sterile sheath, and sterile ultrasound jelly was used both inside and outside the sheath as an acoustic couplant. An 18-gauge Tuohy needle and epidural catheter set were used (Fig. 40.3). The groin was scanned to reveal the femoral vessels. The Tuohy needle was inserted in long axis toward the femoral nerve. On contact with the nerve, 0.5 mL 2% lidocaine with 1:200,000 adrenaline was injected and observed to be just outside the perineural space. Minor adjustments were made to the needle tip position, and another 0.5 mL injectate confirmed satisfactory needle tip placement. An additional 9 mL of 2% lidocaine with 1:200,000 adrenaline was injected to dilate the space to accommodate the perineural catheter. The catheter was placed through the needle approximately 2 cm beyond the needle tip. Correct catheter placement was confirmed by observing the location of injectate administered through the catheter. Next, the catheter was tunneled to a site lateral and distal to the insertion site and secured with Steri-Strips (3M, St. Paul, Minnesota, USA) and a transparent dressing. An infusion of 0.25% bupivacaine at a rate of 5 mL per hour was commenced and continued for 3 days post-operatively. The catheter was removed on the third postoperative day.

The patient made an uneventful recovery from anesthesia and surgery and had excellent analgesia provided by a combination of femoral nerve catheter, diclofenac sodium 75 mg twice daily, and 1g paracetamol four times per day. On the first postoperative day, the patient received counseling on heroin cessation and agreed to be placed in a methadone treatment program.



**Figure 40.3 • Image Showing the Equipment used to Place an Ultrasound-Guided Perineural Catheter.**

Note the standard aseptic preparation pack with sterile fenestrated drape, an 18-gauge Tuohy needle, catheter, and attachments (standard epidural kit from B. Braun Medical, Melsungen, Germany). Also note sterile ultrasound gel and a sterile sheath with which to cover the ultrasound probe, providing a sterile interface between patient and ultrasound probe.

## KEY MESSAGES

1. Heroin use and subsequent opioid tolerance reduce the efficacy of opioid analgesics necessitating an alternate approach to acute pain management.
2. A mechanistic approach to pain management identified femoral nerve block as an appropriate component of an analgesic regimen for femur fracture.
3. Femoral nerve block formed a component of the multimodal analgesic regimen used in this case, which also consisted of NSAIDs and paracetamol.
4. Ultrasound guidance facilitated the precise placement of needle, injectate, and catheter adjacent to the femoral nerve.
5. Regional anesthesia should ideally be performed only when patients are able to report symptoms of neural injury.

## QUESTIONS

1. What is meant by the terms opiate tolerance and addiction?

Answer:

- Opioid tolerance is a predictable pharmacological adaptation to continued opioid exposure resulting in a rightward shift in the dose-response curve. Patients require increasing amounts of the drug to maintain the same pharmacological effects.
- Addiction:
  - Psychological dependence: Need for a specific psychoactive substance either for its positive effects or to avoid negative effects associated with its withdrawal.
  - Physical dependence: State of adaptation to a substance characterized by the emergence of a withdrawal syndrome during abstinence

2. Why was the femoral nerve catheter placed only when the initial block had worn off?

Answer: Inadvertent intraneural injection or catheter placement may result in serious nerve injury. Patients will usually report pain or dysesthesia should these occur during catheter placement (patient feedback). A nerve, which has already been blocked with local anesthetic solution, loses patient feedback and therefore, the potential exists to inflict serious nerve injury. It is best practice to allow the initial block to wear off before placing the perineural catheter.

3. Does ultrasound guidance make the practice of regional anesthesia under deep sedation or general anesthesia safe?

Answer: No, occult intraneural injection or intraneural catheter placement resulting in nerve injury is still possible. Conscious patients may report pain or

dysesthesia should this occur. Deep sedation and general anesthesia will abolish this feedback. Real-time ultrasound guidance may detect needle tip position, but it may not prevent an operator-dependent phenomenon such as intraneural injection. It is best practice to perform regional anesthesia in conscious patients.

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# Alzheimer's Disease and Anesthesia

Owen O'Sullivan

## CASE FORMAT: REFLECTION

An 81-year-old, 50-kg woman presented to the emergency department following a fall at home. She was accompanied by her daughter, who witnessed her mother tripping and falling awkwardly on her right side. The patient was in obvious distress when her right hip was moved and appeared to have a swollen and bruised right thigh. She was agitated, and staff had difficulty obtaining a relevant history from her. The patient's vital signs were as follows: blood pressure, 170/80 mm Hg; heart rate, 104 beats per minute; temperature, 36.2°C; and respiratory rate, 20 breaths per minute.

A collateral history from the patient's daughter reveals a recent diagnosis of Alzheimer's disease (AD) following a steady decline in cognitive function over the last 3 years. The patient was also being treated for hypothyroidism and depression. She had an uneventful cholecystectomy 5 years ago. The patient was taking the following medications once daily: donepezil 5 mg, thyroxine 50 µg, and omeprazole 40 mg.

Clinical examination of respiratory and cardiovascular systems was noncontributory, and on neurological assessment, no sensory-motor deficits were found. Intravenous access was established, and samples were taken for full blood count, coagulation profile, urea and electrolytes, thyroid function, and glucose. IV morphine sulphate 5 mg was administered before transferring the patient to the radiology department. Radiology revealed a fractured neck of the femur on the right. A computed tomography brain scan was also performed, which showed no acute changes. The results of the laboratory investigations are summarized in Table 41.1. The patient consented for a bipolar hemiarthroplasty.

At the preoperative assessment, the anesthetist felt that the risks of performing a regional block outweighed the benefits, particularly as it appeared that the patient would be very uncooperative and was unlikely to reliably report symptoms (e.g., paraesthesia). The anesthetist elected to perform the procedure under general anesthetic, supplemented with regional anesthesia. Standard monitoring was applied preoperatively, consisting of pulse oximetry, electrocardiogram, and noninvasive blood pressure monitoring. Anesthesia was induced with fentanyl 50 µg, propofol 80 mg, and vecuronium 6 mg and was maintained with sevoflurane in a mixture of oxygen and air. An orotracheal tube was inserted. After induction, an episode of bradycar-

dia (32 beats per minute) was effectively treated with glycopyrrolate 200 mg, and six boluses of phenylephrine 50 µg were required to maintain a mean arterial pressure of  $\geq 65$  mm Hg. Oropharyngeal temperature was monitored, and a warming blanket as well as warmed intravenous fluids were used.

After the patient's blood pressure was stabilized, a right-sided femoral nerve block was performed, aseptically, under ultrasound guidance. A total of 20 mL of 0.25% levobupivacaine with 100 mg of clonidine was administered. The surgical procedure was well tolerated. Intraoperatively, paracetamol 1 g was administered intravenously.

On completion of the procedure, residual neuromuscular block was reversed with neostigmine (plus glycopyrronium). The patient was extubated at an appropriate point and transferred to the recovery room. The recovery staff felt she was grimacing and bringing her hand to her right thigh. She remained drowsy and disorientated when engaged, not responding to direct questioning about pain. Morphine 2 mg was given intravenously, and after about 50 minutes in recovery, the patient appeared settled and was transferred to the surgical ward. Postoperative analgesia was prescribed as paracetamol 1 g orally/rectally every 6 hours and morphine 5 mg (0.1 mg/kg) intramuscularly as required.

Over the next few days, the patient was more agitated than normal, and the nursing staff found it difficult to assess the patient's pain intensity. After 5 days, the agitation had settled, and the patient was transferred to a rehabilitation unit. She made a good recovery, however, her daughter felt she was more confused and less independent 3 weeks after surgery.

## CASE DISCUSSION

AD is the most common form of dementia, affecting an estimated 5.1 million Americans. In the United States, an estimated \$148 million is spent annually on AD and other dementias; 1 in 8 individuals over 65 years of age has this neurodegenerative disease, rising to almost half aged 85 or older.<sup>1</sup> With life expectancy ever increasing and no cure at hand, the impact of AD in day-to-day medical practice increases each year. The German physician Alois Alzheimer first described the disease in 1906. He noted microscopic changes at autopsy in the brain of a

**TABLE 41.1** Results of Laboratory Investigations

Hb	10.3g/dL (↓)	Na <sup>+</sup>	144 mmol/L
WCC	10.4 × 10 <sup>9</sup> /L	K <sup>+</sup>	4.5 mmol/L
Plt	289 × 10 <sup>9</sup> /L	Urea	8.2 mmol/L (↑)
INR	1.1	Creatinine	122 μmol/L (↑)
APTT	38 seconds	TSH	3.3 mIU/L
Glucose	6.9 mmol/L	Thyroxine	145 nmol/L (↑)

APTT, activated partial thromboplastin time; Hb, hemoglobin; INR, international normalized ratio; K<sup>+</sup> potassium; Na<sup>+</sup>, sodium; Plt, platelets; TSH, thyroid-stimulating hormone; WCC, white cell count.

51-year-old woman who died after 4 years of progressive dementia. His findings included abnormal clumps (amyloid plaques) and tangled bundles of fibers (neurofibrillary tangles), now considered the hallmarks of the disease that bears his name.

AD is a gradually progressive condition. Problems with memory are the first symptoms, with other aspects of cognition and behavior (difficulty performing everyday tasks, understanding, and speaking) developing later in the disease's course. Late-stage symptoms of AD such as anxiety, aggression, and wandering herald the inevitable requirement for total care.

The definitive diagnosis of AD can only be made on post-mortem examination of the patient's brain. The *Diagnostic and Statistical Manual*, 4th edition<sup>2</sup> provides one example of many criteria used to diagnose probable AD (Table 41.2).

The exact pathogenesis of the disease remains unknown, however, it is thought that the loss of cholinergic neurons in the forebrain basal nuclei plays a central role in the characteristic memory and learning deficits.<sup>3</sup> The etiology of AD is also unknown, however, several risk factors have been identified. The most important of these is advancing age and family history (particularly in early-onset AD). A number of specific genes have been implicated in the development of early-onset AD, in which the onset of AD is before 65 years of age. Genetic mutations on chromosomes 1, 14, and 21 have been identified in many of these cases, inherited in an autosomal dominant fashion, which make up less than 5% of all AD cases. Polymorphisms of the apolipoprotein E gene on chromosome 19 have also been identified as altering susceptibility for AD.<sup>4</sup>

In recent years, there has been increasing interest regarding an Alzheimer's-anesthesia link. In vitro studies have shown halothane and isoflurane to promote amyloid oligomerization.<sup>5,6</sup> This process has been replicated in vivo in transgenic mice, however, it did not result in additional cognitive decline in cognitively impaired mice.<sup>7</sup> To date, human studies have shown no conclusive link between exposure and risk of developing AD.<sup>8,9</sup> Such a link, if one did exist, would be very difficult to demonstrate, largely because anesthesia is administered to facilitate surgery (often emergency), and isolating its effect from other elements such as the surgical stress response can be difficult. Although the patient described herein showed subjective evidence of deterioration postoperatively, keep in mind that AD is a progressive disorder, and deterioration is inevitable.

**TABLE 41.2** Diagnostic Criteria for Alzheimer's Type Dementia

#### Multiple Cognitive Deficits Involving

##### A. Memory impairment and one or more of the following:

- Aphasia
- Apraxia
- Agnosia
- Disturbance of executive functioning

##### B. With impairment and a significant decline in social or occupational functioning as a result of these deficits

##### C. A gradual onset and continuing cognitive decline

##### D. Not caused by

- Other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson's disease)
- Systemic conditions known to cause dementia (e.g., hypercalcemia, hypothyroidism)
- Substance-induced conditions

##### E. Not occurring exclusively during the course of a delirium

##### F. Not better explained by another psychiatric disorder (e.g., a major depressive disorder, schizophrenia)

Adapted from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Arlington, VA: American Psychiatric Association, 1994.



**TABLE 41.3** General Considerations Regarding Anesthesia for the Elderly

Pharmacological Considerations	Other General Considerations
Reduced minimum alveolar concentration	Increased likelihood of ischemic heart disease and cerebrovascular insufficiency
Reduced intravenous anesthetic dose requirements	Decreased lung volumes
Increased proportion of body fat	Decreased response to hypercapnia and hypoxemia
Reduction in skeletal muscle	Increased closing capacity
Reduced renal clearance	Increased incidence of atelectasis and postoperative respiratory tract infections
Reduced hepatic metabolism and albumin production	Deep vein thrombosis is more common
Increased $\alpha$ -glycoprotein production	Increased incidence of diabetes mellitus
Of particular importance in positioning:	Impaired hearing
Limited joint movement	Increased intraoperative heat loss
Weak bones	
Thin skin	

There is no cure yet for AD. The mainstay of symptomatic treatment at present is the use of cholinesterase inhibitors (donepezil in this case), which increase the amount of acetylcholine available in the depleted cholinergic nerves. In terms of anesthetic considerations, these drugs have systemic cholinergic features. This can translate into reduced heart rate variability and increased susceptibility for bradycardia, as we saw in this patient. Extreme bradycardia should be treated with an anticholinergic drug, which does not cross the blood-brain barrier (e.g., glycopyrrolate). Cholinesterase inhibitors also appear to antagonize the effects of neuromuscular blocking agents.<sup>11</sup>

Preoperative assessment should involve the patient's family or caregivers, as the patient's ability to understand, communicate, and cooperate may be significantly impaired. Explanations and questions should be simple and stated in a clear fashion. Multiple comorbidities are common in this age group, and time may be required to establish these as well as to ascertain the patient's regular medications. In a trauma patient with poor communication, efforts should be made to rule out concealed injury (e.g., rib fractures, intracranial trauma). If agitation is a major feature, small amounts of judiciously administered benzodiazepine may be required.

Acquiring consent for patients with AD can prove difficult. It is up to the doctor to establish the patient's capacity to understand information and make an informed decision or seek consent from a relevant other. There is no clear standard or formal guideline available at present. Wishes of relatives and any advance directives should be taken into consideration. Legal aspects relating to consent also vary in different jurisdictions. A diagnosis of dementia does not automatically assume incompetence. AD is progressive; therefore, in early stages, patients will retain enough cognitive capacity to consent themselves. The difficult task is to establish at what point a patient be protected from making a "bad decision." It is not clear whether the patient in this case retained sufficient cognitive function to make an informed decision or whether an effort to establish competence was made. This was certainly a deficiency in her management. It would seem unlikely that the otherwise uncooperative, agitated patient was able to give a meaningful consent.

In preparing for anesthesia, each patient should be evaluated on an individual basis taking into consideration comorbid conditions and the procedure itself. Regional techniques can be challenging because of poor cooperation and agitation,

however, they allow minimal disturbance of mental capacities. Sedative premedications may worsen confusion and agitation. Monitoring should take into account potential of poor functional reserve. General considerations of anesthesia in the elderly should be taken into account (Table 41.3).

Pain management may be challenging and is often undertreated in elderly patients with cognitive impairment. One study of elderly patients posthip fracture showed that cognitively impaired patients received only one-third the amount of opioid analgesia compared with cognitively intact individuals.<sup>12</sup> Possible reasons for this include poor pain assessment in patients with communication difficulties and concern for using analgesics, which may deteriorate cognitive function or other comorbidities. This is despite the fact that inadequate analgesia can lead to poorer clinical outcomes, cognitive dysfunction, depression, longer hospital stays, and compromised pulmonary function.<sup>13</sup>

Appropriate pain assessment tools should be utilized, using self-reporting (preferable) or nonverbal cues as appropriate to patient's degree of understanding and communication. Facial expression may be affected in late dementia adding further complication to assessment. Once an appropriate tool has been selected, it should be used consistently with regular reassessment. Assessment should include duration of pain relief, ability to ambulate and adequately cough, side effects, and patient satisfaction. Analgesia using an epidural route, local anesthetic infiltration, or peripheral nerve blockade can reduce opioid requirement. If opioids are required, an appropriate route of administration should be chosen. Patient-controlled analgesia may be beyond the cognitive or physical ability of the patient. Intramuscular injection results in slower absorption and possible toxicity with repeated dosing and should therefore be avoided. The use of nonsteroidal anti-inflammatory drugs is often restricted in the elderly population because of altered metabolism and excretion leading to drug accumulation.

Although regional anesthesia techniques were welcome in this case scenario, performing them in an uncooperative patient or under general anaesthesia is questionable. Ultrasound guidance does not protect from intraneural (or intravascular) injection. A better option in this patient would have been an iliacus block. Spread of local anesthetic beneath the iliacus fascia produces a high success rate of anesthesia of both the femoral and lateral cutaneous nerve of the thigh (which inner-

vates the anterolateral thigh, the incision area).<sup>14</sup> As this is a compartment block, it can be performed safely in anesthetized patients. The needle insertion point is high at the patient's thigh in the gutter between the sartorius and quadriceps muscle. A blunt needle is inserted perpendicular to the skin. An initial loss of resistance is identified on penetrating the fascia lata. A second loss of resistance indicates penetration of the fascia iliaca. Performed preoperatively in this case, it would have avoided the need for systemic opioids with associated side effects. To extend the duration of the block, a continuous iliacus block could have been subsequently administered under general anesthesia, leaving an epidural catheter in place and using a standard infusion of local anesthetic solution (e.g., levobupivacaine 0.2% titrated to effect).

### KEY MESSAGES

1. AD is increasing in prevalence with increasing life expectancy.
2. Cholinesterase inhibitors, the mainstay of treatment, have anesthetic implications.
3. Anesthesia should be tailored on an individual basis taking into consideration the degree of patient cooperation as well as comorbid conditions. Patient consent and pain management may be particularly challenging.

### QUESTIONS

#### 1. Has anesthesia been shown to cause AD?

Answer: Despite significant interest into the possibility of anesthesia causing AD, to date, there is no evidence of such a link in humans. However, even if there were a link between the two, this would be very hard to demonstrate because it is difficult to isolate anesthetic factors from other factors surrounding surgery (e.g., pain, surgical stress responses). In vitro studies using halothane and isoflurane have resulted in cellular processes (amyloid oligomerization) that are similar to those thought to cause AD.

#### 2. Can patients with AD consent to surgical procedures?

Answer: Keep in mind that a diagnosis of dementia does not automatically assume incompetence. AD is progressive, and early in the disease, patients may retain enough cognitive capacity to consent themselves. It is the responsibility of the treating doctor to establish whether this capacity has been retained or if consent should be sought from a relevant other. There are no guidelines available at present to aid this process, and importantly, legal aspects of consent vary across different jurisdictions. The wishes of family members and advance directives should also be considered.

#### 3. What elements are important in the postoperative pain management of a patient with AD?

Answer: Appropriate and consistent pain assessment tools should be employed in managing analgesia in patients with AD. Self-reporting is still preferable, however, nonverbal cues may need to be utilized as the disease and communicative abilities deteriorate. Keep in mind that the commonly used nonverbal cue of facial expression will also be affected later in the disease. When an appropriate tool is established, it should be applied regularly, especially during movement and coughing. Side effects attributable to analgesics should also be noted. Opioid-sparing measures such as the use of epidural or peripheral nerve blocks should decrease the likelihood of such side effects. If opioids are required, the most appropriate means of administering them should be chosen. Patient-controlled analgesia devices require an adequate level of cognitive function and physical dexterity to operate. Pharmacologic alterations that occur in the elderly should also be considered.

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# Sickle Cell Disease

Siun Burke

## CASE FORMAT: REFLECTION

A 4-year-old boy was scheduled on the emergency trauma list for a right hand nerve and tendon repair. The boy was of West African origin and had only recently arrived in the country. He sustained a right hand laceration 6 hours previously when he ran into a glass door. On preoperative assessment, the child was pale and irritable; he was complaining of thirst, as he had been kept fasting since arrival to the hospital in preparation for surgery. At 15 kg, he was in the 40th percentile for weight. His mother said he lost about "a cup full" of blood earlier.

There were multiple venipuncture marks on the child's left arm; the pediatrician had difficulty with venipuncture and decided that as the child's operation was imminent, he should have a cannula inserted and blood taken under general anesthesia instead.

Finally, the anesthetist asked the child's mother if there was any family history of blood diseases or problems with general anesthesia. She had limited English and was anxiously trying to calm her son. The child's mother said he was from a healthy family, although he seemed to get coughs and colds more frequently than her other children. He never had a general anesthetic, but other family members had undergone uneventful anesthesia.

Two hours later, after 8 hours of fasting, the operating room finally became available. With routine monitors in place, the child had an uneventful inhalational induction, and a 20-gauge cannula was inserted in his left forearm. A laryngeal mask airway was placed, and the child resumed spontaneous respiration of an oxygen, nitrous oxide, and sevoflurane mixture. The fraction of inspired oxygen was 0.3. Maintenance fluids were commenced at 50 mL per hour. A tourniquet was inflated to 100 mm Hg above the patient's systolic blood pressure, and the surgeon proceeded to repair the tendons and nerves. On closer inspection, the surgeon discovered more extensive injuries than expected and informed the anesthetist that he would require at least 2 more hours of operating time.

An hour later, the child started to become hypotensive. His blood pressure was 70/34 mm Hg and he was tachycardic with a heart rate of 139 beats per minute. His oxygen saturation read 92%, and his temperature was 33.2°C. Information for the patient's arterial blood analysis is shown in Table 42.1.

The patient's inspired oxygen concentration was increased to 70%, he was volume resuscitated with crystalloid and red cell concentrate, actively rewarmed, and the surgery was expedited.

In the recovery room, the child complained of severe pain and continued to have a low oxygen saturation of 91% and PO<sub>2</sub> was 65 mm Hg.

Hemoglobin analysis confirmed that the child had sickle cell disease (SCD). He was transferred to the high-dependency unit, managed with supplemental oxygen, fluid and blood resuscitation, and judicious opioid analgesia.

Two days later, the patient developed shortness of breath, a wheeze, and a high temperature of 39.4°C. His chest radiograph showed a new right upper lobe pulmonary infiltrate (Fig. 42.1). This finding was diagnosed as acute chest syndrome (ACS), and the child was started on ceftriaxone, clarithromycin, and regular paracetamol.

On postoperative day 5, the patient was discharged to the general ward. His family was counseled regarding his sickle cell status, its implications for other family members, and for any future illnesses and general anesthetics the child may have.

## CASE DISCUSSION

Discussion points:

1. Pathophysiology of SCD
2. Preoperative screening for sickle cell status
3. Optimal perioperative management SCD
4. Acute chest syndrome

## PATHOPHYSIOLOGY OF SCD

SCD is an autosomal recessive disease that results from the substitution of valine for glutamic acid at position 6 of the  $\beta$ -globin gene, leading to production of a defective form of hemoglobin, hemoglobin S (HbS). Patients who are homozygous for the HbS gene have sickle cell disease. Patients who are heterozygous for the HbS gene are carriers of the condition (sickle cell trait). Under stressful conditions, carriers may display some clinical manifestations. If both members of a couple are carriers, they have a 25% risk of producing a child who is homozygous for the HbS gene.

**TABLE 42.1** Arterial Blood Analysis

		Normal Values
PO <sub>2</sub>	9.2 kPa	11–14 kPa
PCO <sub>2</sub>	8.5 kPa	4–6.5 kPa
Ph	7.19	7.35–7.45
Bicarbonate	19 mEq/L	22–26 mEq/L
Lactate	4 mmol/L	<2 mmol/L
Hemoglobin	6.4 g/dL	10–12 g/dL

The hallmark of SCD is a group of devastating symptoms known collectively as a *sickle cell crisis*. Sickle cell crises are episodes of pain that occur with varying frequency and are usually followed by remission.<sup>1</sup>

In the case history presented herein, the fact that the patient's siblings were well and underwent uneventful general anesthesia in the past does not preclude this child from having a sickle cell crisis, as the risk of heterozygous parents producing a homozygous child is 25%.

Deoxygenated HbS is 50 times less soluble in blood than deoxygenated adult hemoglobin. Deoxygenation of HbS leads to hydrophobic interactions between HbS molecules causing the classic sickle shape. The sickle-shaped red blood cells have reduced deformability, thereby obstructing the microvasculature. This results in vicious cycle of tissue hypoxia and acidosis, which promotes further sickling.<sup>2</sup> Also the impaired stability of HbS leads to increased breakdown of the molecule resulting in the release of large amounts of toxic iron and heme compounds into the cell. This produces oxidant damage to the cell membrane, disruption of the phospholipid bilayer, protein distribution, and normal membrane function. This results in increased adhesion to the vascular endothelium inducing endothelial damage and dysfunction. The endothelial regulatory



**Figure 42.1 • Chest Radiograph Showing a Right Upper Lobe Infiltrate.**

balance between vasoconstriction and vasodilatation and pro- and anti-coagulation is disturbed, leading to ischemia, vaso-occlusion, and pain.<sup>2</sup>

## Preoperative Screening for Sickle Cell Status

Sickle cell disease is a genetic disorder affecting diverse populations. Those at risk include African, Hispanic Mediterranean, Middle Eastern, and Asian Indian. The perioperative period is a well-recognized and predictable time of disease exacerbations.<sup>3</sup> Preoperative screening of at-risk populations is recommended as a method to decrease perioperative morbidity. A solubility test is used to screen for SCD, a deoxygenating agent is added to the blood, and if 25% or more of the hemoglobin is HbS, the cells will sickle and form a turbid suspension. For confirmation, abnormal samples undergo further testing, either hemoglobin electrophoresis or high-pressure liquid chromatography.<sup>4</sup>

The National Institute for Clinical Excellence guideline on preoperative testing, June 2003, states that all patients of ethnic origin considered to be at risk, whose sickle cell status is unknown, should be offered screening with genetic counseling before anesthesia and surgery.<sup>5</sup> The advantages and disadvantages of preoperative screening for sickle cell status are summarized in Table 42.2. A preoperative screening test for the child in the case history presented herein would have detected his sickle cell status and allowed the anesthetist to tailor an anesthetic that would have avoided any factors that precipitate sickling.

**TABLE 42.2** Preoperative Screening for Sickle Cell Status

### Advantages of Preoperative Screening

- Avoids the potential disaster of a perioperative sickle cell crisis in a patient with undiagnosed sickle cell disease.
- As heterozygous parents and siblings may be asymptomatic, there may not be a family history in patients with sickle cell disease.

### Disadvantages of Preoperative Screening

- Low yield of positive test results.
- Low risk of a crisis if every patient considered at risk for sickle cell disease receives a well-conducted general anesthetic avoiding factors that precipitate sickling.
- Risks of indiscriminate preoperative screening resulting in unnecessary surgical cancellations, surgical delays, duplication of screening, and misdiagnosis.
- Children often consider venipuncture to be the worst part of the hospital experience.
- Lack of appropriate medical follow-up and parental counseling in the busy perioperative period.
- Increased diversity of mixed-race populations with low accuracy of self-reported ethnicity.
- Cost of screening.

The patient had been fasting for several hours preoperatively without intravenous fluids, and intraoperative maintenance fluids were minimal without adjustment for fasting time or blood loss. A tourniquet was used for more than 2 hours, which contributed to hypoxia and acidosis. The operating room was cold, there was no warming apparatus, and the child's temperature dropped significantly. His hemoglobin level was not checked preoperatively.

## Optimal Perioperative Management of Patients With SCD

### AVOID HYPOXIA

As many patients with SCD have impaired oxygen delivery secondary to pulmonary damage, widespread vasculopathy, increased blood viscosity, anemia, impaired vascular regulation, and disturbed nitrous oxide signaling. Controlled ventilation with a high-inspired oxygen concentration would have improved oxygenation in this patient's case.

Although *in vitro* evidence of increased sickling in the presence of acidosis exists, no benefit has been detected from alkalinization. Tourniquet use may increase hypoxia and acidosis, but there are reports of uneventful use in SCD, and each case should be considered independently.<sup>6</sup> Judicious use of a tourniquet at minimal inflation pressures and for the minimum time possible may have reduced the degree of acidosis evident in the child presented in this case.

### HEMOGLOBIN DILUTION

Intravascular dehydration increases hemoglobin concentration and consequently the rate of sickling. All patients should be adequately hydrated preoperatively, and careful attention must be paid to intraoperative fluid balance. However, there is no evidence to support aggressive fluid hydration of patients with SCD.<sup>6</sup> In the case described herein, the child should have been commenced on intravenous fluids preoperatively with careful calculation of pre- and intraoperative fluid deficits.

### DILUTION OF SICKLE CELLS

Perioperative red cell transfusion remains a controversial topic. A large prospective randomized trial published in 1995 found no benefit to aggressive transfusion (HbS <30) compared with a conservative transfusion strategy, but there was a higher incidence of transfusion-related complications<sup>7</sup> (Table 42.3).

### AVOID HYPOTHERMIA

Hypothermia has been suggested as a perioperative trigger for SCD complications, however, there is no publication to demonstrate a link. As normothermia is a basic standard of anesthetic care for the general surgical population, it should also be a goal for patients with SCD.

A preoperative diagnosis of SCD in the case presented herein would have ensured a careful approach to fluid management, accounting for preoperative blood loss and duration of fasting, minimum use of a tourniquet, and strict maintenance of the child's temperature throughout the procedure.

### ACS

ACS is defined as a new lobar infiltration on a chest radiograph accompanied by fever greater than 38.5°C, respiratory

**TABLE 42.3** Perioperative Transfusion in Sickle Cell Disease<sup>8</sup>

Group 1	Children who are currently well and undergoing minor surgery (myringotomy)	No transfusion
Group 2	Children who are currently well and undergoing intermediate surgery (tonsillectomy)	May require top-up transfusion to Hb 8–10 g/dL, HbS level will remain elevated
Group 3	Children with a history of major SCD complications (stroke, ACS) or a history of hospital admissions for painful crises or children undergoing major surgery (intra-abdominal or thoracic procedures)	Exchange transfusion to achieve HbS level <30% Total Hb should not exceed 12 g/dL

ACS, acute chest syndrome; Hb, hemoglobin; Hbs, hemoglobin S; SCD indicates sickle cell disease.

Adapted from Sickle Cell Disease Transfusion; Clinical Guideline Great Ormond Street Hospital for Children, NHS Trust.<sup>8</sup>

distress, or chest pain.<sup>9</sup> It is a frequent cause of hospital admission and the leading cause of mortality in young adult SCD patients. Repeated episodes predispose individuals to chronic pulmonary disease including pulmonary hypertension. The incidence following invasive surgical procedures such as intra-abdominal procedures or joint replacement is approximately 10% to 15%.<sup>10</sup> Risk factors include HbSS genotype, low fetal haemoglobin (HbF) concentrations, and high steady-state leukocyte and hemoglobin concentrations. Nearly half of the patients are in the hospital for a diagnosis other than ACS, with superimposition of the disorder during hospital care. Specific causes can be identified in approximately 38% of patients, infections in 29%, and fat embolism in 9%. Infections are equally divided between bacterial viral mycoplasma and chlamydial infections suggesting a macrolide antibiotic as an important treatment adjunct.<sup>10</sup>

The pathophysiology of ACS is linked to hypoxic pulmonary vasoconstriction. The combination of regional hypoxia and vasoconstriction will not only increase HbS polymerization and sickling but will also increase capillary transit time causing exacerbation of endothelial dysfunction via mediators such as hypoxia, cytokines, and free radical species.

ACS is typically detected 48 hours postoperatively. Prevention requires early mobilization, good control of surgical pain, incentive spirometry, physiotherapy, and attention to pulmonary function. Rates of complications and mortality figures are age dependent, increasing in individuals over 20 years of age.

**TABLE 42.4** Causes of Acute Chest Syndrome

Infectious Causes	Noninfectious Causes
<b>Bacteria</b>	
<ul style="list-style-type: none"> <li>• Pneumococcus</li> <li>• Gram-negative bacteria</li> <li>• Chlamydia pneumonia</li> <li>• Mycoplasma pneumonia</li> </ul>	<ul style="list-style-type: none"> <li>• Pulmonary infarction</li> <li>• Hypoventilation secondary to rib infarction or opioid administration</li> <li>• Fat embolism</li> <li>• Pulmonary edema</li> </ul>
<b>Viruses</b>	
<ul style="list-style-type: none"> <li>• Respiratory syncytial virus</li> <li>• Parainfluenza</li> <li>• Influenza</li> </ul>	

Adapted from Credit Valley Hospital Clinical Practice Guideline. Management of Sickle Cell Disease in Children, 2004.<sup>9</sup>

Treatment involves supplemental oxygenation and ventilatory support as required; bronchodilators should be used to treat bronchospasm and antibiotics if pneumonia supervenes. Inhaled nitric oxide may improve alveolar-arterial oxygen gradients and reduce pulmonary artery pressure (Table 42.4).

### KEY MESSAGES

1. Sickle cell disease is an autosomal recessive disease that results in production of a defective form of hemoglobin, hemoglobin S (HbS). Deoxygenation of HbS causes the classic sickle shape with reduced deformability that obstructs the microvasculature.
2. According to the National Institute for Clinical Excellence guidelines, all patients of ethnic origin considered to be at risk, whose sickle cell status is unknown, should be offered screening with genetic counseling before anesthesia and surgery.
3. Optimal perioperative management of patients with SCD requires avoiding factors that may precipitate a sickle cell crisis (e.g., hypoxia, acidosis, intravascular dehydration, hypothermia, and venous stasis).
4. ACS is the leading cause of mortality in young adults with SCD. It is defined as a new lobar infiltration on chest radiograph accompanied by fever greater than 38.5°C, respiratory distress, or chest pain.

### QUESTIONS

#### 1. Which organs are affected by sickle cell disease?

Answer: Sickle cell disease is a multisystemic disease which impacts many major organs. The kidneys may undergo hypertrophy, develop tubular acidosis, tubular deficiencies, proteinuria, nephritic syndrome, and end stage renal disease. The lungs develop pulmonary hypertension in 5% to 30% of patients. The spleen may undergo autoinfarction and hyposplenism. Skin manifestations include chronic leg ulcers and there may be osteonecrosis of the femoral and humeral heads. The eye may develop retinitis proliferans.

#### 2. By what mechanism does HbS arise?

Answer: HbS arises when a single nucleotide substitution CTG for GAG in the sixth codon of the beta globin gene results in the substitution of phenylalanine for glutamic acid. One in 14 people of African heritage are asymptomatic carriers of sickle cell anaemia. One in 700 newborns of African heritage is affected by sickle cell anaemia.

#### 3. What are the benefits of hydroxyurea treatment in sickle cell disease?

Answer: Hydroxyurea is a cytotoxic drug that reduces the production of red cells containing a high level of sickle haemoglobin which tend to arise from rapidly dividing precursors and favours the production of fetal haemoglobin.<sup>11</sup> The number of white blood cells and platelets are also reduced. The metabolism of hydroxyurea results in the release of nitric oxide which also stimulates HbF production. Increased concentration of HbF results in decreased red cell sludging and vaso-occlusion with subsequent decreased ischaemia and necrosis. An increased production of nitric oxide results in more normal vascular tone and decreased pulmonary artery hypertension. In a study of 299 patients by Charache et al.,<sup>11</sup> the incidence of painful crises reduced from 4.5 to 2.5 per year; the rates of acute chest syndrome and blood transfusion also reduced considerably. After 9 years, there was a 40% reduction in mortality in those who received hydroxyurea. Recommendations for hydroxyurea therapy include patients with frequent pain episodes, history of acute chest syndrome, other severe vaso-occlusive events, or severe symptomatic anaemia.

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# Anaphylaxis

Mansoor A. Siddiqui

## CASE FORMAT: STEP BY STEP

A 27-year-old man was admitted to the accident and emergency department, feeling febrile, with a 1-day history of abdominal pain, nausea, and vomiting for the last 12 hours. He had been fit and healthy in the past and was not taking any medication. The patient smoked 10 cigarettes per day, and drank alcohol occasionally. He had not been eating or drinking for 8 hours before admission and had vomited twice during the preceding 3 hours. He had not undergone surgery in the past and had no known drug allergies.

The patient's examination revealed the following: temperature, 37.8°C; dehydration, mild; heart rate, 110 beats per minute; blood pressure, 90/50 mm Hg; respiratory rate, 20 breaths per minute on auscultation; and normal vesicular breathing. On abdominal palpation, there was tenderness in the right iliac fossa. The patient's airway was evaluated as Mallampati grade I with normal dentition. Investigations showed the following: hemoglobin, 16.8 g/dL; hematocrit, 0.41; white blood cell count,  $13.5 \times 10^9$ ; and platelets,  $198 \times 10$ .

The patient was diagnosed as having acute appendicitis and was scheduled for emergency open appendectomy by the surgical team. An 18-gauge intravenous (IV) cannula was inserted and fluid resuscitation commenced. After receiving 500 mL of Hartmann's solution, the patient's heart rate decreased to 90 beats per minute, and his blood pressure increased to 110/60 mm Hg. A dose of prophylactic antibiotic (co-amoxiclav, 1.2 g) was administered at the surgeon's request and the patient was transferred to the operating room.

After preoxygenation for 3 minutes, anesthesia was achieved using fentanyl 100 µg, propofol 250 mg, and suxamethonium 100 mg as part of a rapid sequence induction. A cuffed oroendotracheal tube (inner diameter, 8.5 mm) was inserted without difficulty and fixed at 23 cm after auscultating for bilateral air entry. Atracurium 40 mg was administered 5 minutes later.

Two minutes after atracurium administration, the patient's airway pressure was noted to increase rendering his lungs progressively more difficult to ventilate. On examination, his face was flushed, and urticarial rashes were observed on his skin. His heart rate was 120 beats per minute, and his blood pressure was 80/40 mm Hg. On auscultation, the patient's chest was wheezy, and air entry decreased bilaterally. Marked facial swelling occurred in 2 to 3 minutes.

## What is the differential diagnosis?

Clinically, it is neither possible nor necessary to differentiate between anaphylaxis and anaphylactic reactions at the time of presentation, as both respond to the same treatment. Symptoms of anaphylaxis have their onset within minutes but occasionally can occur late following exposure to the causative agent. Symptoms can be masked under general anesthesia (Table 43.1).

Individuals with a history of atopy, asthma, or food allergies appear to be at increased risk of latex allergy but possibly not anaphylaxis to neuromuscular-blocking drugs.<sup>5,6</sup> There is evidence that patients receiving β-blockers (showing unopposed α-adrenergic effects and therefore being more resistant to adrenaline) and those with asthma suffer more severe reactions.<sup>13,14</sup>

Additional differential diagnoses to consider include vasovagal reactions. They can mimic anaphylaxis and are characterized by hypotension, bradycardia, pallor, weakness, nausea, vomiting, and diaphoresis. Urticaria, pruritus, angioedema, tachycardia, and bronchospasm, however, are not vasovagal responses.

Acute respiratory decompensation from severe asthma attacks, foreign body aspiration, and pulmonary embolism can mimic respiratory symptoms suggestive of anaphylaxis, but other characteristics such as pruritus, urticaria, and angioedema are lacking.

Seizure disorders, myocardial infarction, and arrhythmias can be readily distinguished clinically. Patients with hereditary angioedema do not exhibit pruritus and urticaria; a family history is usually present.

It is likely that this patient has had an allergic reaction or anaphylaxis to one of the substances he received in the perioperative period.

## What is the pathophysiology of anaphylaxis?

Any drug administered in the perioperative period can cause a severe immune-mediated hypersensitivity reaction after exposure to a foreign protein (antigen) that stimulates immunoglobulin E (IgE) production. Non-immune-mediated reactions account for 30% to 40% of hypersensitivity reactions.<sup>4</sup> They neither involve IgE nor prior exposure to this antigen.

It is not possible to clinically differentiate between immune and non-immune-mediated reactions. Anaphylactoid reactions are more likely to involve skin features (94% vs. 72%),<sup>5,6</sup> and anaphylactic reactions are more severe.<sup>5</sup>

The time course of anaphylaxis can be classified as uniphasic, protracted, or biphasic. Reactions typically follow a



**TABLE 43.1** Clinical Manifestations of Suspected Anaphylactic Reactions

Organ System	Symptom	Sign	Specific Sign During Anesthesia
Cutaneous	Itching	Rash, erythema, flushing, urticaria, angioedema	
Respiratory	Lump in the throat Hoarseness Dysphonia Dyspnea	Stridor Wheezing Pulmonary edema Cyanosis	Difficult to ventilate ↑Peak airway pressure SpO <sub>2</sub> ↑EtCO <sub>2</sub>
Cardiovascular	Angina Light-headedness Faintness	Tachycardia Arrhythmias Hypotension Cardiac arrest	↓ EtCO <sub>2</sub> ↑Hematocrit ST segment, T-wave changes
Gastrointestinal	Nausea Abdominal pain	Vomiting Diarrhea	

Adapted from Soetens FM, Vercauteren MP. Allergic reactions during anaesthesia: diagnosis and treatment. *Jurnalul Roman de Anestezie Terapie Intensiva* 2008;15:43–50.

uniphasic course, that is, they respond rapidly to treatment and do not recur. In some patients, symptoms may fail to improve or may worsen as the effect of adrenaline wears off (protracted anaphylaxis); however, 20% will be biphasic in nature.<sup>7</sup> The second phase usually occurs after an asymptomatic period of 1 to 8 hours, but there may be a delay of up to 24 hours. Prolonged observation in these cases is needed.<sup>8</sup>

### How would this case be managed intraoperatively?

Anaphylaxis is a medical emergency that requires immediate treatment. Even a severe anaphylactic reaction is associated with a prompt and successful response to appropriate treatment in most patients. This patient should be managed aggressively according to the existing Association of Anaesthetists of Great Britain and Ireland guidelines.<sup>3</sup>

1. Stop administration of all agents likely to have caused anaphylaxis.
2. Call for help.
3. Maintain airway, give 100% oxygen, and lay patient flat with legs elevated.
4. Give epinephrine (adrenaline). This may be given intramuscularly in a dose of 0.5 mg to 1.0 mg (0.5 to 1 mL of 1:1,000) and may be repeated every 10 minutes according to the arterial pressure and pulse until improvement occurs. Alternatively, 50 to 100 µg intravenously (0.5 to 1 mL of 1:10,000) over 1 minute has been recommended for hypotension with titration of further doses as required.
5. Start rapid IV infusion with colloids or crystalloids. Adult patients may require 2 to 4 liters of crystalloids.

Secondary therapy consists of:

1. Antihistamines (chlorpheniramine 10 to 20 mg by slow IV infusion)

2. Corticosteroids (100 to 500 mg hydrocortisone IV slowly)
3. Bronchodilators may be required for persistent bronchospasm

The patient was immediately commenced on 100% oxygen. With help on the way, the adrenaline ([1:10,000], 50–100 µg over 1 minute) was administered, followed by two additional increments. A rapid infusion of 0.9% sodium chloride was started. The patient was positioned supine with the legs slightly elevated. At this point, his blood pressure increased to 100/50 mm Hg. His airway pressure normalized, and ventilation of his lungs was once again easy. The surgery was restarted, and the patient was stabilized, chlorpheniramine 10 mg was administered by slow IV infusion. Hydrocortisone 100 mg was administered intravenously. At this point, the patient was hemodynamically stable with a heart rate of 90 beats per minute, blood pressure of 110/70 mm Hg, and clear chest on auscultation. His skin looked normal. Surgery proceeded to laparotomy because of peritonitis. The surgeon requested muscle relaxation.

### What would be the additional management of choice?

In terms of anaphylactic risk, neuromuscular blocking agents (NMBAs) could be classified into three groups: high risk (succinylcholine and rocuronium), intermediate risk (vecuronium, pancuronium), and low risk (mivacurium, atracurium, cisatracurium).<sup>2</sup>

As cross-reactivity between NMBAs occurs in up to 60% of patients, no other agent should be used without prior testing.<sup>2</sup> Thus, the best additional prophylactic strategy would be to avoid using NMBAs, which implies an attempt to deepen anesthesia, taking advantage of muscle relaxation produced by inhalational agents. If this step fails to provide adequate relaxation, and bearing in mind that succinylcholine is the most likely culprit in this scenario, a short-acting low-anaphylactic-

risk NMBA such as mivacurium may be used. This drug may have the extra advantage of not requiring reversal, thus minimizing further histamine release. Pretreatment with antihistamines and corticosteroids in this case may limit the severity of potential reactions, although there is currently little evidence to support their routine use for this sole purpose.

Following administration of mivacurium 8 mg, surgery was finished quickly, and the patient's trachea was extubated uneventfully.

A blood sample (5–10 mL) was taken in three plain bottles for mast cell tryptase measurement. The first sample was taken about 15 minutes after the event, the second after 1 hour, and the third after 6 hours. The samples were spun, separated, and refrigerated at 4°C for testing within 48 hours (can be stored at –20°C for longer).

### How would this patient be managed postoperatively?

Posttreatment observation of these patients is required, because of the potential for the second phase of reactivity. The anesthetist should take responsibility in investigating the patient for the cause of anaphylaxis.

This patient was admitted to the high-dependency unit overnight. The serum concentration of mast cell tryptase taken 1 hour after the reaction was 27 ng/mL (normal <1 ng/mL).

This abnormal result confirms that the patient had an anaphylactic reaction, but it does not identify the cause. Serum mast cell tryptase measurement has a positive predictive value for the diagnosis of anaphylaxis of 95.3% and a negative predictive value of 49%.<sup>6</sup> Thus, a negative test does not rule out anaphylaxis completely. Also, tryptase levels are unlikely to be elevated in mild systemic reactions.

The patient should be advised about the importance of further testing before discharge. For these tests, the patient is sent to an allergologist in a regional allergy center. The radioallergosorbent test is a technique for measuring antigen-specific antibodies in serum. If a fast result is needed, this is the test of choice based on the fact that the concentration of specific IgE antibodies is the same during the reaction as after 4 to 6 weeks.<sup>16</sup>

Skin tests (which may take the form of skin prick or intradermal tests) should be done 6 weeks after the reaction. Before 4 weeks, the intracellular stocks of histamine and other mediators are still lower than normal, therefore increasing the probability of a false-negative result. For the same reason, drugs that could modify the skin's response have to be avoided (e.g., antihistamines, angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, vasoconstrictors, neuroleptics). Because of the risk of life-threatening reactions, challenge tests are not done except for local anesthetics.<sup>15</sup>

A copy of the entire patient's records (i.e., copies of anesthetic chart, drug charts, full details of reaction, and reports of tests done) is sent to both the allergologist and the general practitioner. In addition:

- Patients and their family members are to be informed about the incident. A full account of the events, a written record of the reaction, and advice regarding future anesthetics should be given. The patient is encouraged to carry an anesthetic card or medic alert bracelet.

- The primary and attending team, if different, are also informed about the incident and are given a copy of case notes.
- The National Medicines Board or appropriate body should be informed regarding the incident. A national database may allow physicians to determine the precise incidence of allergic reactions to various substances relative to their market share, thus making comparisons between countries possible.
- The case is discussed at a departmental mortality and morbidity meeting. Ideally, a departmental policy regarding follow-up and a standard checklist of actions should be designed and implemented.

### KEY MESSAGES

1. Anaphylaxis is a severe, potentially fatal systemic allergic reaction with a variable clinical picture. There is no valid predictor of anaphylaxis, and previous exposure is not necessary.
2. Epinephrine in incremental doses is the mainstay of early treatment.
3. Further evaluation, diagnostics, and reporting are highly desirable in the interest of the patient and the anesthetist when faced with subsequent surgery. Diagnosis is made with intraoperative tests (mast cell tryptase) and postoperative tests (radioallergosorbent tests for specific IgE antibodies and skin tests).

### QUESTIONS

1. What is anaphylaxis and what is its incidence during anesthesia?

Answer: Anaphylaxis is a severe allergic reaction to any stimulus, usually having sudden onset and usually lasting less than 24 hours, involving one or more body systems and producing one or more symptoms such as hives, flushing, itching, angioedema, stridor, wheezing, shortness of breath, vomiting, diarrhea, and shock. The incidence of anaphylaxis is estimated to be between 1 in 10,000 and 1 in 20,000 anesthesia cases.

2. Which substance is most often associated with anaphylactic reactions during anesthesia?

Answer: Any substance or drug administered in the perioperative period can potentially produce life-threatening immune-mediated hypersensitivity reactions. Neuromuscular blocking agents (55%), latex (22.3%), and antibiotics (14.7%) are the substances most frequently associated with anaphylactic reactions.

3. What are the principles of intra- and postoperative management of anaphylaxis?

Answer: Anaphylactic reactions cannot be clinically distinguished from non-immune-mediated reactions (which account for 30%–40% of hypersensitivity reactions). Therefore, any suspected anaphylactic reaction must be extensively investigated using combined

peri- and postoperative testing to confirm the nature of the reaction, to identify the causative substance, and to provide recommendations for future anesthetics.

Guidelines have been issued by the Association of Anaesthetists of Great Britain and Ireland to standardize the emergency treatment of anaphylaxis.<sup>3</sup> These are:

- a. Stop administration of all agents likely to have caused anaphylaxis.
- b. Call for help.
- c. Maintain airway, give 100% oxygen and lay patient flat with legs elevated.
- d. Give adrenaline. This may be given intramuscularly in a dose of 0.5 mg to 1 mg (0.5 to 1 mL of 1:1000) and may be repeated every 10 minutes according to the arterial pressure and pulse until improvement occurs.

Alternatively, 50 to 100 µg intravenously (0.5 to 1 mL of 1:10,000) over 1 minute has been recommended for hypotension with titration of further doses as required.

- e. Start rapid IV infusion with colloids or crystalloids.

Secondary therapy consists of:

1. Give antihistamines (chlorpheniramine 10—20 mg by slow IV infusion)
2. Give corticosteroids (100—500 mg hydrocortisone IV slowly)
3. Bronchodilators may be required for persistent bronchospasm.

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# Persistent Postsurgical Pain

Peter John Lee

## CASE FORMAT: REFLECTION

A 64-year-old woman presented to her general practitioner with a lump in the left upper quadrant of her left breast. On examination, a hard nodule was detected, and she was referred to a general surgeon for further investigation. Mammography and breast biopsy confirmed the presence of a 3-cm invasive adenocarcinoma. Computed axial tomography showed no evidence of metastatic disease. The patient was scheduled for a left mastectomy and axillary node clearance.

The patient had previously undergone a total abdominal hysterectomy under general anesthesia. She was taking pravastatin 20 mg daily for dyslipidemia but was otherwise fit and healthy. She was anxious at the postoperative interview and was particularly apprehensive about pain after her operation, as she had experienced considerable pain following her hysterectomy.

Physical examination of the patient was unremarkable apart from the lump in her left breast, and the results of a full blood picture, urea, and electrolytes were all normal. Her electrocardiogram and chest radiograph were unremarkable.

Before surgery, and with standard monitoring in progress, a paravertebral block was performed on the patient. The third thoracic vertebral body was identified with the patient in a sitting position, and, under aseptic conditions, following local infiltration, a 22-gauge Tuohy needle was inserted 3 cm lateral to the most cephalad aspect of the spinous process. The needle was advanced to 3.5 cm to make contact with the transverse process. The needle was then "walked" above the transverse process until a loss of resistance to air confirmed the correct location. A catheter was inserted into the paravertebral space, and following a test dose, bupivacaine 0.5% 20 mL was administered.

Anesthesia was induced using propofol 180 mg, and muscle relaxation was achieved with atracurium 35 mg. Following tracheal intubation, anesthesia was maintained with inhaled sevoflurane in an air/oxygen mixture.

Paracetamol 1000 mg and diclofenac 75 mg were administered intravenously during surgery. Surgery was completed within 1 hour, and the patient's trachea was extubated following reversal with glycopyrrolate and neostigmine.

In the postanesthesia care unit, the patient reported a pain score of 4, in which a score of 0 represented no pain,

and 10 represented the worst possible pain. The patient was prescribed paracetamol 1000 mg and diclofenac sodium 75 mg as required. The paravertebral block catheter was removed before she was transferred to the ward.

On the first postoperative day, the patient complained of mild pain while at rest and moderate-to-severe pain during physiotherapy and while mobilizing. The paracetamol was discontinued, and the patient commenced on co-codamol (codeine phosphate 15 mg/paracetamol 500 mg). The patient reported some relief from pain at rest and was discharged on the fourth postoperative day.

Three months later, after an outpatient consultation, the surgical team reported that the patient complained of moderate pain in the left axilla for which she took paracetamol and ibuprofen. She was referred to a pain specialist for further treatment.

## CASE DISCUSSION

Persistent postsurgical pain (PPSP) is defined as pain that developed after a surgical procedure, is of at least 3 months' duration in which other causes for the pain have been excluded, and whereby the possibility that the pain is continuing from a preexisting problem has been explored and excluded.<sup>1</sup> Women who undergo breast surgery experience chest wall, breast, or scar pain (11%–57%), phantom breast pain (13%–24%), and arm and shoulder pain (12%–51%). The incidence of pain in one or more of these sites is close to 50% 1 year after breast surgery for cancer.<sup>2</sup>

### Risk Factors for PPSP

There are several risk factors for PPSP<sup>3</sup> (Table 44.1).

*Demographic and Psychosocial Factors* Age is a risk factor for the development of PPSP. The incidence of PPSP after mastectomy is 26% in patients older than 70 years, 40% in those 50 to 69 years, and 65% in those 30 to 49 years.<sup>4</sup> Preoperative anxiety, although a predictor of clinically meaningful acute pain,<sup>5</sup> is not an independent contributor to the prediction of either the presence or the intensity of PPSP after breast surgery.<sup>6</sup> Prescribing an anxiolytic in this case could have relieved the patient's anxiety and decreased acute postoperative pain.

**TABLE 44.1** Risk Factors for Persistent Postsurgical Pain

- |   |
|---|
| 1. Demographic and psychosocial factors |
| 2. Preoperative pain                    |
| 3. Type of surgery                      |
| 4. Concomitant treatments               |
| 5. Genetic factors                      |
| 6. Postoperative pain                   |

**Preoperative Pain** The evidence on preoperative pain as a risk factor for PPSP is conflicting. A retrospective study showed a significant correlation between preoperative breast pain and phantom breast syndrome.<sup>7</sup> A prospective trial found no correlation between preoperative breast pain and the risk of developing PPSP.<sup>6</sup>

**Type of Surgery** PPSP is more common after breast-conserving surgery than after radical surgery.<sup>8</sup>

**Concomitant Treatments** There is a higher incidence of PPSP in patients who undergo chemotherapy<sup>9</sup> or radiotherapy.<sup>6</sup> The patient in this scenario would certainly undergo chemotherapy or radiotherapy following surgery.

**Genetic Factors** A genetic influence on the development of PPSP has been shown in animals.<sup>10</sup> Three genetic variants of the gene encoding catechol-O-methyltransferase have been identified, and five combinations of these variants are strongly associated with variation in the sensitivity to experimental pain and with the development of a long-term pain disorder.<sup>11</sup>

**Postoperative Pain** Severe acute pain after breast surgery is a risk factor for the development of PPSP,<sup>6</sup> and adequacy of postoperative analgesia is an important determinant of PPSP.<sup>12</sup>

## Decreasing the Incidence of PPSP

Peripheral and central sensitization of the nervous system is implicated in the development of PPSP. Nociception-induced hyperalgesia observable in the postoperative period is a consequence of surgical tissue and nerve trauma.<sup>13</sup> Nociceptive inputs alter subsequent sensory nervous system processing, both peripheral and central.<sup>14</sup> This neuroplasticity is initially excitatory (termed *sensitization*) and develops from activation (acute, transient, and activity-dependent) via modulation (subacute, slower, still reversible functional changes) through to modification (chronic structural and architectural changes).<sup>15</sup> Nociceptive excitatory neuroplasticity is expressed clinically as increased sensitivity to pain. Peripheral nervous system excitation increases sensitivity to painful stimulus in the area of damaged tissue.

## Changes Underlying the Development of PPSP

Providing adequate postoperative analgesia after breast surgery decreases the incidence and intensity of PPSP. Because it has

been theorized that PPSP results from sensitization, the blockade of sensitization by regional technique may help with prevention. Paravertebral block for breast surgery decreases the incidence of pain symptoms, the intensity of motion-related pain, and the intensity of pain at rest at 12 months.<sup>15</sup> Multimodal analgesia with gabapentin and topical application of a eutectic mixture of local anesthetic decreases the postoperative analgesic requirements and the incidence and intensity of PPSP 3 months after breast surgery.<sup>16</sup> Multimodal analgesia using a continuous paravertebral block and regular acetaminophen and parecoxib decreased the incidence of PPSP at 10 weeks.<sup>12</sup>

Although satisfactory analgesia at rest was achieved in this case, movement-evoked pain was described as moderate to severe and was not treated adequately. The paravertebral catheter could have been left in situ, and an infusion of local anesthetic could have been administered postoperatively or a combination of nonsteroidal anti-inflammatory drugs and paracetamol with opioids administered regularly. The use of multimodal analgesia techniques, which has been shown to provide optimal dynamic pain relief with minimal side effects, may prevent PPSP.

The perioperative use of tricyclic antidepressants and anti-convulsants may also benefit in the prevention of PPSP. The antiepileptic drugs gabapentin and pregabalin are efficacious in the treatment of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia.<sup>17</sup> Pregabalin binds to the alpha<sub>2</sub>delta subunit of calcium channels, reducing depolarization-induced calcium influx and thereby decreasing the release of excitatory neurotransmitters, including glutamate, noradrenaline and substance P.<sup>17</sup> A single dose of gabapentin administered to patients before mastectomy decreases postoperative morphine consumption and pain during movement.<sup>18</sup> Gabapentin, as part of a multimodal analgesic regimen, decreased the incidence of PPSP at 10 weeks after breast surgery.<sup>19</sup> Gabapentin could certainly have been used in this case.

Excitatory neurotransmitters, acting through N-methyl-D-aspartate receptors, are implicated in the process of sensitization and development of PPSP. Ketamine, an N-methyl-D-aspartate receptor antagonist, is an antihyperalgesic drug that modulates excitatory neurotransmission, decreasing both mechanical hyperalgesia around the wound and incidence of residual pain in patients undergoing bowel surgery.<sup>20</sup> As part of a multimodal analgesic technique along with intraoperative epidural anesthesia, ketamine reduces the incidence of PPSP 1 year after major digestive surgery.<sup>21</sup>

There are no specific recommendations regarding the use of ketamine in this scenario.

Perioperative administration of the N-methyl-D-aspartate receptor antagonist amantadine did not prevent the development of postmastectomy pain syndrome in patients who underwent breast surgery with axillary lymph node dissection.<sup>22</sup>

## KEY MESSAGES

1. The incidence of PPSP following breast surgery is 48%.
2. Severe acute postoperative pain is the most significant risk factor for PPSP after breast surgery.

3. Multimodal analgesic techniques, including conduction blockade by regional technique, reduce the incidence and severity of PPSP.
4. The gabapentinoid antiepileptic drugs (gabapentin and pregabalin), and the N-methyl-D-aspartate receptor antagonist ketamine show promise in perioperative prevention of PPSP.

## QUESTIONS

### 1. What is the definition of PPSP?

Answer: PPSP is defined as pain that developed after a surgical procedure, is of at least 3 months' duration in which other causes for the pain have been excluded, and whereby the possibility that the pain is continuing from a preexisting problem has been explored and excluded.

### 2. What techniques have been successfully used to reduce the incidence of PPSP after breast surgery?

Answer: Providing adequate postoperative analgesia after breast surgery decreases the incidence and intensity of PPSP. Multimodal analgesia using continuous paravertebral block and regular acetaminophen and parecoxib, or a eutectic mixture of local anesthetic and gabapentin has decreased the incidence of PPSP after breast surgery.

### 3. In what way might pregabalin prevent sensitization of the pain system?

Answer: Pregabalin binds to the  $\alpha_2\delta$  subunit of calcium channels in neurons, reducing depolarization-induced calcium influx and thereby decreasing the release of excitatory neurotransmitters, including glutamate, noradrenaline, and substance P at the level of the dorsal horn.

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# Opioid-Induced Hyperalgesia

James O'Driscoll

## CASE FORMAT: REFLECTION

A 29-year-old, ASA II (American Society of Anesthesiologists), 80-kg male admitted to the plastic surgery department sustained significant injuries to his right hand while as a passenger in a car involved in a road traffic accident. He had extensive lacerations to both the palmar and dorsal aspects of his right, dominant hand and had clinical evidence of tendon and nerve damage. He also had fractures of the first and second phalanges of his third finger. It was therefore proposed to explore and repair the wound under anesthesia.

The patient had a history of intravenous (IV) drug abuse (heroin) but was not currently using and had been abstinent for 2 months. He also had a history of long-term, well-controlled asthma and was using salbutamol and beclomethasone metered-dose inhalers. His examination was unremarkable.

The various options for anesthesia including general, regional, and combined techniques were discussed with the patient. He requested a general anesthetic and refused all offers of regional/nerve blockade despite explanation of these techniques and reassurance regarding efficacy and safety.

On arrival in the operating room, appropriate monitoring was established, and after preoxygenation with 100% oxygen, anesthesia was induced with 2  $\mu$ g midazolam, 250 mcg fentanyl, and 300 mg propofol. A size 4 laryngeal mask airway was placed, and the position was confirmed by auscultation and capnography. Anesthesia was maintained uneventfully with sevoflurane in an oxygen/air mixture and assisted ventilation in a pressure support mode until return of spontaneous ventilation. Analgesia administered consisted of 2 g paracetamol IV, 75 mg diclofenac IV, 15 mg morphine IV, and wound infiltration by a surgeon at end of the procedure with 10 mL 0.25% bupivacaine. The total anesthesia time was 3 hours, and the patient's vital signs were stable throughout.

After the procedure, the patient was transferred to the postanesthesia care unit (PACU), and 10 minutes later, he began to complain of pain. His Verbal Rating Scale score was 8 out of 10 (scale, 0–10), his pulse was 110 beats per minute, and noninvasive blood pressure was 140/88 mm Hg. Further bolus doses of morphine were administered to a total of 10 mg in accordance with PACU protocol. Twenty minutes later the patient complained again of pain and was reviewed by the anesthetist. He gave the patient two further

boluses of 5 mg morphine and noted that the pain seemed out of proportion for the procedure given the multimodal approach taken, particularly the local infiltration. The patient's Verbal Rating Score at this stage remained at 8, his heart rate was 100 beats per minute, and noninvasive blood pressure was 140/94 mm Hg. As soon as the patient had settled, he was discharged from the PACU to the general ward on oral paracetamol and diclofenac around the clock as well as oxycodone as required for breakthrough pain.

Two hours later, the anesthetist was called to review the patient's pain on the ward. The patient reported increased pain scores (Verbal Rating Score, 7) and had not responded to oral analgesia in the form of oxycodone. His heart rate was 110 beats per minute and noninvasive blood pressure was 150/88 mm Hg. Morphine-based patient-controlled analgesia was prescribed in addition to regular paracetamol as well as nonsteroidal anti-inflammatory drugs, and the patient seemed to have improved when reviewed 1 hour later.

In the morning, the acute pain team reviewed the patient, and he reported moderate pain control. Examination of the patient-controlled analgesia delivery system showed a total consumption of 120 mg of morphine over 16 hours and a bolus demand/delivery ratio of 4:1. It was felt that his pain control was suboptimal despite all the appropriate measures.

The patient subsequently made a full recovery and never demonstrated any evidence of a return to IV drug abuse. In the weeks following surgery, the patient reported that pain control was excellent.

## CASE DISCUSSION

The finding of increased postoperative pain and postoperative opioid consumption in a patient receiving a high rather than a low intraoperative opioid dose indicates the possibility of opioid-induced hyperalgesia (OIH) in this patient. Alternatively, this patient may have experienced acute tolerance to analgesic opioid effects. No firm conclusions can be drawn. Differentiation between OIH and tolerance requires a method directly assessing pain sensitivity, and implementing such a method into clinical practice is difficult.

### OIH

OIH is a phenomenon whereby opioid drugs prescribed to alleviate pain may paradoxically make the patient more sensitive

to painful stimuli. There is strong animal evidence for the phenomenon particularly with long-term opioid administration.<sup>1</sup> There is, however, a growing body of evidence for its occurrence in humans. OIH is most commonly described in the setting of long-term use or withdrawal from long-term use as is the case of the patient described herein.<sup>2</sup> Increased pain sensation after opioids for acute pain has also been reported, particularly with remifentanyl.<sup>3</sup>

Various potential mechanisms have been proposed, but none appears to be definitive. There may be sensitization of peripheral nociceptors, enhanced production and release, or decreased reuptake of nociceptive neurotransmitters, or sensitization of second-order neurons. We do know that c-fos expression is increased and that blockade of N-methyl-D-aspartic acid or excitatory amino acid receptors prevent hyperalgesia associated with opioid use.<sup>4</sup>

## Management of OIH

The first step is to have a high index of suspicion and to identify patients who may be at risk of developing OIH. Currently, this group would mainly be those on long-term opioid therapy. Any opioid has the potential to cause OIH. A multimodal approach to analgesia is essential, as the use of adjuvants (regional anesthesia, clonidine, ketamine) attenuates/blocks the development of OIH.<sup>4</sup>

There was potential for improvement in the management of our patient. It would be important to discover the exact reasons for patient refusal of regional anesthesia (even just as adjuvant) and to address his concerns in an attempt to change his mind. It is very likely that a brachial plexus block would have provided optimal intra- and postoperative analgesia in his case. Perhaps the addition of other drugs such as clonidine or ketamine may have helped once pain control was found to be unsatisfactory in the PACU. Gabapentin has been shown to prevent OIH in rats, explained by the fact that neuropathic pain and OIH share common pathophysiologic mechanisms.<sup>5</sup> Another important observation is that OIH is often related to a particular drug in a particular patient. Therefore, rotating drugs both in the acute and long-term pain setting can help to reduce this phenomenon.<sup>4</sup> As soon as a high-dose, opioid-induced hyperalgesic effect is suspected, dose reduction of the causative agent and/or switching to another opioid agonist (in this case fentanyl or sufentanyl) is a logical next step.

### KEY MESSAGES

1. OIH is a pronociceptive phenomenon that can occur with acute or long-term opioid administration.
2. Disappearance of opioid treatment effects coupled with unexplained pain expansion may indicate OIH.

3. The cornerstone of managing OIH is dose reduction of the culprit opioid and the use of multimodal analgesia.

## QUESTIONS

1. What is OIH, and in what clinical settings is it likely to occur?

Answer: OIH is a clinical condition whereby opioid drugs such as morphine or any opioid drug prescribed to relieve pain may paradoxically increase the patient's perception of pain. The exact mechanism by which this occurs is unknown, but there is strong evidence for the involvement of several nociceptive pathways and regulatory mechanisms such as the excitatory amino acids and N-methyl-D-aspartic acid receptor. OIH has most often been described in the setting of long-term pain, in patients with prolonged exposure to opioid medication. It has also been described following acute exposure to opioids such as remifentanyl.

2. Can OIH be prevented?

Answer: Little is known about the exact mechanism, thereby making strategies for prevention difficult. It is known that a multimodal approach to analgesia in both the acute and chronic settings is essential. This also limits exposure to opioid medications and all their undesirable effects.

3. What is the treatment for OIH?

Answer: Treatment of OIH can be difficult when it does occur. Keep in mind that reducing the dose or changing to a different opioid can help alleviate the problem. Drug rotation is becoming a common strategy in the long-term use of opioids for pain management to maintain efficacy and reduce side effects. In addition, clonidine and ketamine may be added to the armamentarium of pain management in these cases.

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# Transurethral Resection of Prostate Syndrome

John Dowling

## **CASE** FORMAT: STEP BY STEP

A 74-year-old, 92-kg man (American Society of Anesthesiologists II with long-standing, well-controlled hypertension) was admitted for transurethral resection of prostate (TURP) for benign prostatic hypertrophy. He had an uneventful inguinal hernia repair under general anesthesia 8 years previously. His medications included a  $\beta$ -adrenergic antagonist (bisoprolol) and an HMG Co-A reductase inhibitor (pravastatin).

The patient underwent a full preoperative evaluation including a past medical and anesthetic history and relevant physical examination. Table 46.1 summarizes his preoperative blood results. The patient's preoperative electrocardiogram (ECG) reading was normal.

### **What are the main anesthetic considerations for this patient?**

TURP is performed by passing a loop through a special cystoscope (resectoscope). Using direct visualization and continuous irrigation, prostatic tissue is resected by applying a cutting current to the loop. This procedure is performed on a predominantly elderly population, therefore, anesthesia carries a mortality risk of 0.2% to 6%, which correlates best with the American Society of Anesthesiologists' physical status scale. Although this patient is on statins, because he is 74 years old, he has a high chance of cerebrovascular and cardiovascular atherosclerotic disease. In addition, being hypertensive increases his risk of perioperative myocardial events because of possible left ventricular hypertrophy. His ECG reading, however, was normal. Despite the fact that  $\beta$ -blockers reduce the patient's ability to compensate for hypotension, they should be continued in the perioperative period, as they have proven benefit in terms of perioperative morbidity/mortality in patients with ischemic heart disease.

A neuraxial block is considered the most suitable technique for TURP, although general anesthesia has a similar morbidity and mortality profile. A subarachnoid block to T10 is desirable, as it provides excellent anesthesia without important hypotension for the patient and adequate perineal and pelvic floor relaxation for the surgeon. Compared with general anesthesia, regional anesthesia appears to reduce the incidence of postoperative deep venous thrombosis, and it is less likely to mask signs of bladder perforation symptoms or TURP syndrome.

As there were no contraindications to a neuraxial anesthetic technique, a spinal anesthetic was planned for the procedure and discussed with the patient.

Upon arrival at the operating room, a wide-bore (16-gauge) cannula was inserted in the patient's left wrist, and 500 mL of Hartmann's solution was administered. Standard monitoring was instituted (ECG, oxygen (O<sub>2</sub>) saturation, and noninvasive blood pressure monitoring). Forty percent O<sub>2</sub> was administered via a Venturi fixed performance mask. A spinal anesthetic was performed at the level of L3 to L4 with the patient in the sitting position under strict aseptic conditions. Three mL of 0.5% hyperbaric bupivacaine was injected into clear, free-flowing cerebrospinal fluid. After 10 minutes, a motor and sensory block to the level of T10 was noted and deemed adequate for starting the procedure. The attending anesthesiologist kept in regular verbal contact with the patient. A senior surgical trainee began the procedure with his consultant surgeon supervising at chair side. Baseline monitoring (immediately post-spinal blockade) showed a heart rate of 66 beats per minute, blood pressure of 114/74 mm Hg, O<sub>2</sub> saturation of 99%, and the patient's ECG trace showed normal sinus rhythm.

Fifty minutes into the procedure, the patient complained of a headache and dizziness and was noted to be somewhat confused and restless. His heart rate was found to have fallen to 52 beats per minute, and he was noted to be hypertensive (blood pressure, 162/106 mm Hg). The patient became progressively more anxious and in addition was now dyspneic. He then complained of feeling cold, and a subsequent temperature measurement showed him to be markedly hypothermic (33.8°C).

### **What differential diagnosis should be considered at this stage?**

- TURP syndrome
- Hypoxia
- Hemorrhage
- Myocardial infarction
- Cerebrovascular event
- Hypothermia
- Bladder perforation
- Septicemia (gram-negative)

### **What is the most likely diagnosis, and how could this be rapidly ascertained?**

The most likely diagnosis is TURP syndrome and could be confirmed via a stat sodium (showing hyponatremia).

**TABLE 46.1** Preoperative Blood Results

Measured Variable	Preoperative Value	Normal Range
Na <sup>+</sup>	136	135–146 mEq/L
K <sup>+</sup>	4.1	3.5–5.0 mEq/L
Creatinine	0.087	0.06–0.12 mmol/L
Urea	4.4	2.5–6.7 mmol/L
Hemoglobin	14.7	14–17 g/dL
White blood cells	5.7	4.3–10.8 × 10 <sup>9</sup> /L

The classic triad of features that constitute the TURP syndrome are (a) dilutional hyponatremia, (b) fluid overload with consequent pulmonary and cerebral edema, and (c) glycine toxicity.<sup>1</sup>

In the TURP procedure, resecting prostatic tissue opens up the large and extensive network of prostatic venous plexuses. Continuous irrigation is used to distend the bladder and remove blood and tissue from the operative view. A hypo-osmotic glycine solution is most commonly utilized for this purpose because of its favorable optical and electrical properties in transurethral surgery. A variable amount of this irrigating solution will be absorbed intravascularly over the course of the procedure. Absorption of large amounts of this fluid (>2 L) results in a constellation of symptoms commonly described as TURP syndrome.

The critical physiologic derangement of central nervous system function is not only hyponatremia, but also acute hypo-osmolality because the blood-brain barrier is largely impermeable to sodium but freely permeable to water. The cerebral edema caused by acute hypo-osmolality can increase intracranial pressure with consequent bradycardia, hypertension, and neurologic symptoms.<sup>1</sup>

#### What factors influence the volume of solution absorbed intravascularly?

1. Hydrostatic pressure, which is determined by the height of the irrigating fluid above the patient. The irrigating bag must be kept as low as possible to achieve adequate flow of irrigant (usually 60–70 cm).
2. Number and size of opened venous sinuses
3. Procedure duration and experience of the operating surgeon. The most important preventive measure during surgery is preserving the prostatic capsule. Violation of the capsule aids entry of irrigation fluid into the periprostatic and retroperitoneal space.
4. Venous pressure: More fluid is absorbed if the patient is hypovolemic or hypotensive.<sup>2</sup> Of note, smoking is the only patient factor known to be associated with large-scale fluid absorption during TURP.<sup>9</sup>

#### What are the origins and manifestations of the classic triad of symptoms?

1. Dilutional hyponatremia found in TURP syndrome is a hypervolemic hyponatremia representing excess total

body water with normal total body sodium. In general, if the serum sodium concentration falls to 120 mEq/L, signs and symptoms of dilutional hyponatremia may ensue.

2. Fluid overload may give rise to pulmonary edema and cardiac failure especially in individuals with preexisting cardiovascular compromise, as well as cerebral edema.
3. Glycine toxicity results in impairment of consciousness and transient blindness. This is thought to be related to glycine acting as an inhibitory neurotransmitter at both central nervous system and retinal sites.<sup>1</sup>

#### What other signs and symptoms may indicate the presence of or an evolving TURP syndrome?

1. Cardiovascular system: The presence of hypertension and bradycardia may reflect a hypervolemic state; hypotension may then ensue representing emerging cardiac failure. In addition, glycine is known to be directly cardiotoxic to the myocardium.
2. Central nervous system: Confusion and agitation progressing to unconsciousness reflects hyponatremia, cerebral edema, and glycine toxicity.
3. Pulmonary system: Fluid overload may result in pulmonary edema and hypoxemia.
4. Hematologic system: Dilutional anemia may ensue.
5. Nausea and vomiting may result from hyperammonemia—in severe cases progressing to encephalopathy (ammonia is a major by-product of glycine metabolism).
6. Hypothermia may occur as a result of using a cold irrigant solution.<sup>3</sup>

An arterial blood gas analysis was quickly performed, and the results are shown in Table 46.2.

#### How could the most obvious abnormalities be explained?

The patient's Na<sup>+</sup> measurement of 111 mEq/L reflects a decrease in serum Na of 25 mEq/L. A diagnosis of TURP syndrome can be made on the basis of the arterial blood gas findings. Typically, if the serum Na<sup>+</sup> levels drop to below 120 mEq/L, signs and symptoms of water intoxication will be seen.<sup>1</sup> In addition, the blood gas shows that the patient was

**TABLE 46.2** Intraoperative Arterial Blood Gas

Measured Value	Result	Normal Range
pH	7.38	7.35–7.45
pO <sub>2</sub>	9	11–14.5 kPa
pCO <sub>2</sub>	4.8	4.5–6.0 kPa
Na <sup>+</sup>	111	135–146 mEq/L
K <sup>+</sup>	4.7	3.5–5 mEq/L
Cl <sup>-</sup>	102	100–106 mEq/L
Base excess	1.2	-2–+2
Hemoglobin	12.6	14–17 g/dL

hypoxemic ( $PO_2$  of 9), indicating respiratory compromise and probable pulmonary edema. A dilutional anemia is also seen (hemoglobin level of 12.6), reflecting the large intravascular fluid load.

### What would be the emergency management in this case?

Treating TURP syndrome depends on early recognition, and therefore, the anesthetist should maintain a high degree of clinical vigilance. Initial management should follow the airway breathing and circulation guidelines (ABC). The operating surgeon should be informed, and the procedure should be discontinued as soon as sites of bleeding have been controlled.<sup>5</sup> Cardiovascular compromise including bradycardia and hypotension may require treatment with anticholinergic and/or adrenergic agents, particularly in this case, in which the patient has been on  $\beta$ -blocker therapy.

Subsequently, the surgery was rapidly terminated, and the patient was monitored in the recovery room. His  $SpO_2$  was between 92% and 95% on a Venturi face mask delivering 60%  $O_2$ . A 12-lead ECG was performed, which showed widening of the QRS complex on the ECG trace (Fig. 46.1).

### What arrhythmias and other cardiac manifestations may be seen in a patient with TURP syndrome?

When serum sodium levels fall to less than 120 mEq/L, signs of cardiovascular depression can occur; less than 115 mEq/L may cause bradycardia, widening of the QRS complex, ST-segment elevation, ventricular ectopic beats, and T-wave inversion.<sup>3</sup> A serum sodium level of less than 110 mEq/L may cause respiratory and cardiac arrest.

The patient subsequently developed severe respiratory distress and was unable to maintain adequate  $O_2$  saturations on high-flow  $O_2$ .

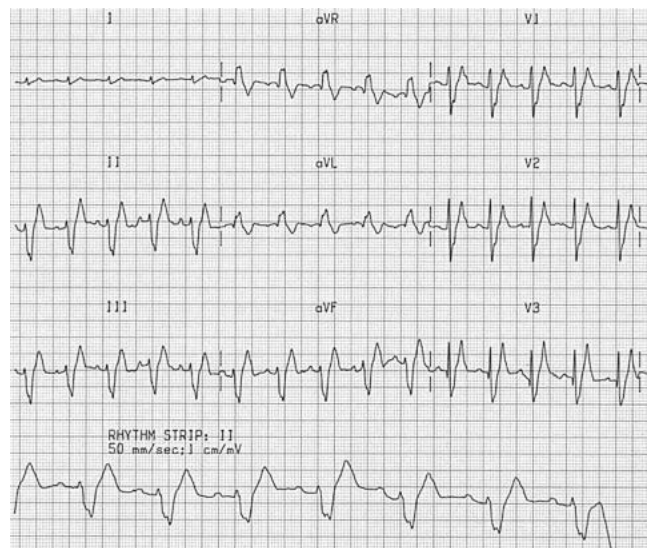


Figure 46.1 • QRS Widening on Electrocardiogram.

A diagnosis of pulmonary edema was made on the basis of clinical and radiology findings (Fig. 46.2). The patient was intubated, and transfer to the intensive care unit was arranged. He was ventilated using a synchronized intermittent mandatory ventilatory mode. He was also started on a hypertonic saline infusion to slowly correct his hyponatremia (at a rate of approximately 1 mmol/L per hour). When hemodynamically stable, the patient was started on a bolus of intravenous furosemide to treat his fluid overload and consequent pulmonary edema. Twenty-four hours later, the pulmonary edema and hyponatremia had resolved, the patient was extubated, and he made an uneventful recovery.

### What are the current controversies regarding treatment of TURP syndrome?

In the past, fluid restriction was suggested as a potential therapy to improve hyponatremia, yet this method did not address the hypovolemia and low cardiac output that frequently followed the discontinuation of irrigating solution. Several studies support the use of hypertonic saline in the correction of the existing hyponatremia.<sup>2,3</sup> Treatment is recommended when measured serum sodium is below 120 mEq/L or when there are obvious signs and symptoms of hyponatremia. In addition, studies have shown a higher frequency of neurological disability and death among individuals who either did not receive or when there was a delay in instituting hypertonic saline therapy.<sup>6</sup> As a general rule, a correction of serum sodium by 1 mmol/L per hour may be considered as a safe rate but should be guided by improvements in the patient's neurological status. Hypertonic saline 3% is suggested as an initial fluid therapy, which can be adjusted in relation to serial serum sodium measurements and clinical improvement of the patient. Hypertonic saline has been shown to counteract



Figure 46.2 • Pulmonary Edema.

cerebral edema and expand plasma volume; the theoretical risk of causing pulmonary edema has not been seen in clinical usage.<sup>7</sup>

Although the risk of pontine myelinolysis is more immediate in the setting of chronic hyponatremia, the literature still advocates a gradual sodium correction even in the acute phase.<sup>6</sup>

Intravenous furosemide may be used to counteract the acute pulmonary edema and promote diuresis. No studies advocate its routine use in the treatment of fluid absorption, and in fact, it may exacerbate a preexisting hyponatremic hypovolemic picture. In situations when pulmonary edema is not established, the best practice is probably to withhold furosemide until the patient is hemodynamically stable and a hypertonic saline infusion has been started.<sup>8</sup>

Preventive measures, such as low-pressure irrigation, might reduce the extent of fluid absorption but do not eliminate this complication. Alternative surgical techniques, such as the use of bipolar resectoscopes and prostate vaporization may influence fluid absorption and its consequences.

#### KEY MESSAGES

1. Absorption of small amounts of fluid occurs in 5% to 10% of patients undergoing TURP and results in an easily overlooked mild TURP syndrome.
2. Most symptoms appear 30 to 45 minutes after surgery is completed, at which time hyponatremia is explained by natriuresis and not by dilution. However, symptoms related to fluid absorption develop in 3% to 5% of patients.
3. Furosemide should be used cautiously. In the absence of pulmonary edema, its use should be best delayed until the patient is hemodynamically stable and hypertonic fluid therapy has been instituted.  
Judicious correction of hyponatremia with hypertonic saline has been shown to improve patient outcome.

#### QUESTIONS

1. What key precautions can surgeons and anesthesiologists take to prevent the occurrence of TURP syndrome?

Answer: The likelihood of developing TURP syndrome can be lessened by limiting the surgical procedure's duration, by reducing the height and thus pressure of the irrigating solution, by attempting to preserve the prostatic capsule during the resection, by ensuring the patient is optimally hydrated preoperatively, and compensating for intraoperative blood loss (often difficult to appreciate). As continuous absorption of irrigating fluid may be assumed, only minimal volumes of Na containing maintenance intravenous fluids should be infused during the procedure.

2. What is the main advantage of performing the procedure under neuraxial blockade rather than general anesthesia?

Answer: With the patient awake, it is possible to keep in constant verbal contact with him and thus detect any early signs of confusion or restlessness, which may indicate an evolving TURP syndrome. This aspect of patient monitoring is lost with general anesthesia.

3. What are the attributes of an ideal irrigation fluid for TURP? How are these similar to those that are currently available?

Answer: The ideal irrigation fluid should be optically clear, nonelectrolytic (and therefore nonconductive of the electro-surgical current) and isotonic. Numerous nonconductive fluids are available, such as glycine 1.5%, sorbitol 3%, mannitol 5%, and sterile water. The most commonly used irrigation fluid, glycine 1.5% solution is optically clear and non-electrolytic but hypo-osmolar (200 mOsm/L); therefore, large amounts may be absorbed systemically through the vascular prostate bed. Direct toxicity and metabolism of glycine can account for some of the neurologic symptoms of TURP syndrome. The 6-carbon alcohols, mannitol and sorbitol, both act as osmotic diuretics, in slightly varying concentrations. Solutions approximating 3% of either of the 6-carbon alcohols are most often used. These solutions are purposely prepared moderately hypotonic to maintain their transparency. Sterile water offers a very clear view of the operating field (and is therefore often used for cystoscopy), but it is highly hypotonic and may result in hemolysis of erythrocytes and possible renal failure when absorbed in large amounts through vascular openings.

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# Anesthesia and Sleep-Disordered Breathing

Leon Serfontein

## CASE FORMAT: STEP BY STEP

A 47-year-old, 5' 7", 85-kg (body mass index, 29.4 kg/m<sup>2</sup>) male was scheduled for a semiurgent posterior cervical discectomy following acute C7–8 disc herniation with radicular symptoms to his right hand.

The patient had a history of chronic “neck problems” requiring intermittent use of nonsteroidal anti-inflammatory drugs for analgesia. He had no other medical problems of note. He had smoked 10 to 15 cigarettes a day for 20 years. Ten years previously, he had undergone general anesthesia for an inguinal hernia repair, after which he had awoken with a very sore, hoarse throat. He was told subsequently that it had been “very difficult to insert the breathing tube.” No notes or further details of the event were available. The patient was taking an herbal throat spray at night, which he believed helped reduce snoring.

On examination, the patient was of stocky build and slightly overweight with a potentially difficult airway on assessment (Mallampati grade III, thyromental distance 6 cm, a short neck with a large circumference and limited mobility especially on extension). His blood pressure was 150/90 mm Hg, and his pulse rate was 85 beats per minute. All other clinical observations were normal.

The laboratory investigations were as follows: full blood count, hemoglobin, 16.8 g/dL; hematocrit, 0.51; platelets,  $218 \times 10^9/L$ ; electrolytes, normal. The electrocardiogram reading showed no abnormalities.

### What conclusions derived from the assessment could have important implications for this patient’s perioperative management?

- The likelihood of difficulty in airway management and/or intubation.
- High suspicion of previously undiagnosed obstructive sleep apnea (OSA). The presence of polycythemia may indicate severe OSA (Table 47.1).

### What is the relationship between difficult intubation and OSA?

Patients with difficult airways are at substantially increased risk of OSA.<sup>3</sup> Conversely, the possibility of difficulty with

airway management and intubation should be considered in patients with known or suspected OSA.<sup>4</sup>

OSA is a syndrome characterized by periodic, partial, or complete obstruction of the upper airway during sleep. There are practice guidelines for the perioperative management of patients with OSA.<sup>16</sup> A good starting point is to stratify the patients using the terms mild, moderate, and severe as defined by the laboratory where the study was done.<sup>16</sup>

### Which important details in the patient’s history need to be investigated to support the diagnosis of OSA?

Symptoms and signs of OSA are listed in Table 47.1. The strongest of these associations are snoring, witnessed apneas, and obesity. Other risk factors include male gender,<sup>12</sup> aging,<sup>13</sup> menopausal status,<sup>14</sup> black race,<sup>15</sup> alcohol, and smoking.

### Given the fact that no formal diagnosis of OSA can be made at this time, how should this patient be managed?

This patient should be managed as if he has OSA. Up to 20% of adults have at least mild OSA.<sup>6</sup> In a substantial number of these patients, the condition remains undiagnosed and untreated.<sup>5</sup>

Ideally, the severity of OSA may be determined by sleep studies. If a sleep study is not available, such patients should be treated as if they have moderate sleep apnea unless one or more of the signs or symptoms is severely abnormal (e.g., markedly increased body mass index or neck circumference, respiratory pauses that are frightening to the observer), in which case they should be treated as if they have severe sleep apnea.<sup>16</sup> In addition, polycythemia in this patient’s case may indicate severe OSA.

If a sleep study had been done, the results should be used to determine the perioperative anesthetic management of a patient. Because procedures differ among laboratories, the American Society of Anesthesiologists’ Task Force on Perioperative Management of Patients with OSA recommends that stratification of OSA should be done using the terms none, mild, moderate, or severe as defined by the laboratory where the study was done rather than the actual apnea-hypopnea index (the number of episodes of sleep-disordered breathing per hour). If this is not indicated, it may be approximated as shown in Table 47.2.

An anesthetic plan was discussed with the patient. He was told that an awake fiberoptic-assisted intubation would be

**TABLE 47.1** Symptoms<sup>7,9</sup> and Signs<sup>10</sup> Associated With Increased Risk of Obstructive Sleep Apnea<sup>11</sup>

Snoring (prominent, habitual)	Obesity
Witnessed apneas (gaspings/choking)	Increased neck circumference
Excessive/persistent daytime sleepiness	Hypertension
Family history	Presence of difficult airway predictors
	Right heart failure*
	Polycythemia*

\*Severe obstructive sleep apnea.

performed. The patient was very anxious and requested premedication. Diazepam 10 mg was prescribed orally.

**Assuming that the patient is likely to suffer from OSA, what would be the advantages of using an asleep technique for instrumenting the airway?**

Provided that spontaneous ventilation is maintained, or the ability to ventilate the patient is confirmed before a long-acting muscle relaxant is given, advantages include: (a) eliminating the need for sedation (awake technique) and (b) the ability to better gauge the potential for or the degree of obstruction and the likelihood of requiring devices to improve airway patency postoperatively (e.g., nasal airway, continuous positive airway pressure machine).

**What are the main considerations regarding the choice of drugs used for anesthesia and analgesia in this patient in the perioperative period?**

- Premedication with sedatives or opioids should ideally be avoided.
- Drugs used during general anesthesia should be chosen and dosed in such a way to minimize the extent and duration of any inhibitory effect on this patient's ability to maintain normal airway patency and ventilation postoperatively.
- The provision of adequate postoperative analgesia should be accomplished in a multimodal fashion to reduce the need for opioids. This includes the use of paracetamol, nonsteroidal anti-inflammatory drugs, and local anesthetics for incision infiltration. This patient would have conceivably benefited from wound infiltration with a long-acting local anesthetic.

In the anesthetic induction room on the morning of surgery, a 14-g cannula was inserted. Midazolam 4 mg and fentanyl 100 mg were given intravenously in incremental doses, as well as glycopyrrolate 200 µg. Following topicalization of

**TABLE 47.2** Stratification of Patients with Obstructive Sleep Apnea<sup>9</sup>

Severity of OSA	Adult AHI	Pediatric AHI
None	0–5	0
Mild OSA	6–20	1–5
Moderate OSA	21–40	6–10
Severe OSA	>40	>10

AHI, apnea-hypopnea index; OSA, obstructive sleep apnea. Reproduced with permission from Gross JB, Bachenberg KL, Benumof JL, et al. Practice guidelines for the perioperative management of patients with obstructive sleep apnea: a report by the American Society of Anesthesiologists Task Force on Perioperative Management of patients with obstructive sleep apnea. *Anesthesiology* 2006;104:1081–1093.

the airway, an orotracheal tube 8.5 was inserted with fiberoptic assistance. Anesthesia was induced with propofol and maintained with sevoflurane delivered in a mixture of 50:50 oxygen:nitrous oxide. Vecuronium 8 mg was given for muscle relaxation. Following prone positioning, the surgery proceeded uneventfully and was finished 2 hours later. Throughout the course of the surgery, the patient received paracetamol 2 g, diclofenac sodium 75 mg, and morphine 8 mg intravenously.

**What are the important safety considerations when extubating this patient's trachea?**

- Full reversal of neuromuscular blockade should be ensured and neuromuscular recovery should be ascertained (preferably with a nerve stimulator) before extubation.
- Extubation should occur with an oral or nasopharyngeal airway in place and only after spontaneous ventilation is established and the patient is conscious (rousable).
- The preferred recovery position for the patient is the lateral posture.<sup>1</sup> Placing his head in the sniffing position and displacing the mandible forward will further reduce the tendency for airway collapse.<sup>2</sup>
- Continuous positive airway pressure therapy should be applied if obstruction occurs despite the simple measures mentioned in this list (and in all cases of diagnosed OSA whereby the therapy has been prescribed or used preoperatively).

After reversal of neuromuscular blockade, the patient was extubated awake in the supine position. In the recovery area, he complained of pain and was given a further 4 mg of morphine in incremental doses. He desaturated a number of times to as low as 92%, and the anesthesiologist decided that supplemental oxygen should be continued on the ward. After a stable period of around 45 minutes, the patient was sent back to the ward. Approximately 6 hours after admission to the ward, the patient was found by a nurse to be unarousable, with minimal breathing efforts and a SpO<sub>2</sub> of 70%. His radial pulse was palpable, and his blood pressure was 85/55 mm Hg.

After an unsuccessful attempt at intubation by the anesthetic trainee on call, a laryngeal mask airway was inserted, and a total of 800 mcg naloxone was given in increments intravenously. The patient responded well to these measures over the course of the next 20 minutes. He subsequently removed the laryngeal mask airway himself. The patient was taken to the intensive care unit fully conscious with a SpO<sub>2</sub> of 96% on a 35% oxygen mask and recovered from the event with no permanent sequelae.

### What simple measures could have minimized/prevented this complication?

- Although supplemental oxygen is mandatory in the postoperative period, to the inexperienced observer, this may mask the presence of obstructive episodes by reducing recurrent desaturation. This may have been the case in this patient.
- Patient positioning: The literature supports an improvement in apnea-hypopnea index scores when adult patients with OSA sleep in the lateral, prone, or sitting positions rather than the supine position in the nonoperative setting. This would suggest that positional measures may be of use to prevent airway collapse even in the postoperative setting, although the literature does not provide specific guidance in this regard. It is unclear if this patient was encouraged to maintain a sitting or lateral posture postoperatively.
- An appropriate postoperative nursing environment is crucial. This patient should have ideally spent his recovery period in a high-dependency area. Airway patency was likely to deteriorate postoperatively because of residual levels of anesthetic agents, opioid analgesics, or drugs used for sedation.
- Monitoring: The literature is insufficient to offer guidance regarding the appropriate duration of postoperative respiratory monitoring in patients with OSA. However, hospitalized patients who are at increased risk of respiratory compromise from OSA should have continuous pulse oximetry monitoring after discharge from the recovery room. If frequent or severe airway obstruction or hypoxemia occurs during postoperative monitoring, initiating nasal continuous positive airway pressure or nasal intermittent positive pressure ventilation should be considered.<sup>16</sup>

### Would there be an alternative to benzodiazepines in this case?

Gabapentin, as a potential multimodal perioperative drug, would have been a more suitable drug choice. Since its introduction in 1993 as an adjunctive anticonvulsant, its use has extended into more acute situations, particularly in the perioperative period.

Gabapentin is known to decrease preoperative anxiety; significantly lower Visual Analog Scale anxiety scores have been shown in patients given gabapentin as opposed to placebo before knee surgery.<sup>17</sup> Gabapentin has been proven to blunt hemodynamic response to laryngoscopy and intubation. Patients receiving 800 mg of gabapentin 1 hour before surgery had significantly decreased mean arterial pressure and heart rate during the first 10 minutes after endotracheal intubation compared with either 400 mg gabapentin or placebo.<sup>17</sup>

A meta-analysis of gabapentin administration for acute postoperative pain showed that a single preoperative dose of

### KEY MESSAGES

1. OSA is a syndrome characterized by periodic, partial, or complete obstruction of the upper airway during sleep.
2. Patients with difficult airways are at substantially increased risk of OSA.<sup>3</sup> Conversely, the possibility of difficulty with airway management and intubation should be considered in patients with known or suspected OSA.<sup>4</sup>
3. Practice guidelines exist for the perioperative management of patients with OSA.<sup>16</sup> They target the preoperative assessment (risk stratification) and preparation, intraoperative (choice of anesthesia technique), and postoperative management (analgesia, oxygenation, patient positioning and monitoring).

gabapentin 1200 mg or less decreased pain intensity at 6 and 24 hours postoperatively. Twenty-four-hour cumulative opioid consumption was also significantly reduced.<sup>17</sup>

It is likely that this patient would have benefited from gabapentin 900 mg administered 1 to 2 hours before surgery, and the advantages include anxiolysis, decreased pressor response to intubation, and less acute postoperative pain. Repeated doses, however, carry the risk of increased sedation and withdrawal phenomenon.

Another option for this patient would have been a remifentanyl infusion used for sedation during fiberoptic intubation.

### QUESTIONS

#### 1. How is OSA defined?

Answer: OSA is defined as cessation of airflow for >10 seconds despite continuing ventilatory effort, 5 or more times per hour of sleep, and usually associated with a decrease in SaO<sub>2</sub> of >4%.

#### 2. What symptoms and signs are associated with an increased risk of OSA?

#### 3. Which predictors for difficult mask ventilation are commonly associated with OSA?

Answer: History of snoring, obesity, and advanced age are commonly associated with OSA.

Snoring (prominent, habitual)	Obesity
Witnessed apneas (gaspings/choking)	Increased neck circumference
Excessive/persistent daytime sleepiness	Hypertension
Family history	Presence of difficult airway predictors
	Clinical features of right heart failure*
	Clinical features of polycythemia*

\*Severe OSA.

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# Herbal Medicine and Anesthesia

Ashit Bardhan and Craig Dunlop

## CASE FORMAT: REFLECTION

A 33-year-old woman presented at term in spontaneous labor, requesting analgesia. She had previously had a normal vaginal delivery, during which she had received effective epidural analgesia. She had no significant medical problems, had experienced an uneventful pregnancy, had no allergies, and denied taking any medications. Epidural analgesia was offered and informed consent was obtained.

After establishing intravenous access, an epidural catheter was inserted aseptically on the first attempt in the L3–4 interspace. Effective analgesia was obtained. The patient had an uneventful labor and gave birth about 6 hours later to a live male infant by normal vaginal delivery. Before discharge from the labor ward, the epidural catheter was removed. She remained an inpatient for another day before being discharged home.

The following day at home, the patient began to develop central back pain and an associated headache. Both were relieved with simple analgesia including paracetamol and diclofenac. She did not seek medical attention at this point. The headache did not recur, but the back pain returned and gradually increased in severity over the subsequent 48 hours. By this stage, she was in severe pain with restricted mobility and presented to the emergency department for review. She was afebrile and generally well, reported no altered sensation or weakness of the lower limbs, and no symptoms of bladder or bowel disturbance. Examination revealed tenderness over the epidural insertion site with no neurologic signs in the lower limbs. She required opiate analgesia to provide effective pain relief.

The patient's blood test results were as follows: hemoglobin, 12.6 g/dL; white blood cell count,  $13.5 \times 10^9/L$  (elevated); neutrophils,  $10.22 \times 10^9/L$  (elevated); platelets,  $220 \times 10^9/L$ ; erythrocyte sedimentation rate, 83 mm/hr (elevated); international normalized ratio, 1.0; activated partial thromboplastin time, 30 seconds; sodium, 133 mmol/L; potassium, 3.9 mmol/L; urea, 4.8 mmol/L; and serum creatinine, 64 mmol/L.

A differential diagnosis of epidural abscess or epidural hematoma was considered, and the patient was admitted for further investigation and analgesia. An urgent neurosurgical consultation was requested, and a magnetic resonance imaging scan of the lumbar spine was performed (Fig. 48.1).

The magnetic resonance imaging scan revealed an epidural hematoma located at L3–4 with significant thecal

sac compression. In the absence of objective neurologic signs, the patient was managed conservatively, with analgesia as required and mobilization as tolerated.

The patient's history was reviewed for possible risk factors for epidural hematoma. At this stage, she admitted to taking oral Arnica when labor began to "reduce perineal bruising and aid healing following delivery." She had omitted to mention this at the time, as she felt that herbal remedies were safe and were not classified as medicines. By the time of the epidural insertion, she had taken three doses of two tablets. Examination of the packaging revealed no information as to active constituents. An Internet search suggested that Arnica montana contained "coumarin derivatives" and may potentiate anticoagulant effects. More formal evidence was limited to a journal letter stating that ingestion may result in an anticoagulant effect from coumarin constituents.<sup>1</sup>

The patient's symptoms improved over the course of 4 days, and she was discharged home. She was reviewed 3 weeks later and had complete pain resolution.

## DISCUSSION

Complementary and alternative medicine is increasing in popularity, encompassing herbal and dietary supplements as well as alternative medical theories such as homeopathy and traditional Chinese medicine. Estimates of usage in patients vary from 4.8% to 42%.<sup>2–6</sup> Of these percentages, approximately 70% of patients are thought to not routinely disclose their usage to medical staff,<sup>4</sup> as in the patient described in this case. The danger lies with the assumption that the term *natural* is synonymous with *safe*. A survey of herbal medicine use in parturients showed that only 14.6% of those using herbal remedies considered them to be medications.<sup>2</sup>

Although the therapeutic profile of Arnica provides a possible explanation as to the occurrence of epidural hematoma in the patient in this case, a causal relationship could not be retrospectively ascertained. Also, she would have been likely to be offered an epidural even if the information regarding Arnica usage had been provided. A coagulation screen before insertion may have been prudent.

Under United States law, herbal and homeopathic medications are classified as dietary supplements, thus exempting them from regulations applicable to the introduction of prescription medicines.<sup>7</sup> The effect of this classification is to reinforce the belief that they are not drugs and additionally has



**Figure 48.1 • Magnetic Resonance Image of the Spine, Lateral View.**

removed the incentive to generate evidence for therapeutic or adverse effects. The presence and concentration of active constituents is often extremely difficult to assess and may vary among brands.<sup>8</sup> Licensing requirements in the United Kingdom are somewhat more rigorous but still fall short of preclinical animal and controlled clinical trials considered standard in the pharmaceutical industry.<sup>9</sup>

Of the more well-known supplements, the effects of most concern in the perioperative period are those of cardiovascular instability, drug interactions, altered coagulation, and altered sedation. Ephedra (ma-huang) may precipitate hypertension and has been associated with cerebrovascular accidents, arrhythmias, myocardial infarction, and sudden cardiac death.<sup>10–12</sup> Garlic and ginkgo may alter platelet aggregation and prolong bleeding times,<sup>13</sup> while ginseng may have a procoagulant effect.<sup>14</sup> Kava, St. John's Wort, and Valerian root may all increase sedative effects and prolong emergence.<sup>13</sup> Diet may also provoke serious adverse effects. Grapefruit juice is known to inhibit cytochrome CYP3A4, which plays a role in metabolism of statins and in this setting, may precipitate rhabdomyolysis.

Traditional Chinese herbal medicine may be even more challenging in that patients may be prescribed complex combinations of ingredients, leading to difficulty in assessment of what they are actually taking. Additionally, these herbal medicines commonly contain significant contaminants, such as heavy metals.<sup>15</sup> One of the few prospective studies investigating outcomes followed a cohort of 601 patients in Hong Kong

and examined the incidence of adverse events in the perioperative period.<sup>16</sup> In their population, 80% of patients took self-prescribed traditional Chinese herbal medicine, and they found an increased risk of adverse effects in the preoperative period including hypokalemia and prolonged activated partial thromboplastin time. No significant association was found between the use of any type of traditional Chinese herbal medicine and the occurrence of either intraoperative or postoperative events.

There is little information regarding guidelines for managing patients taking herbal medications in the perioperative period. The American Society of Anesthesiologists has published a leaflet for doctors containing information about more commonly encountered substances,<sup>7</sup> as well as an information leaflet for patients.<sup>17</sup> Awareness of the risks and direct questioning, along with patient education, remain the cornerstone of management.

### KEY MESSAGES

1. The use of herbal medicine is often not reported to medical staff.
2. Although often assumed to be "natural" and thus innocuous, herbal medicines may potentially have significant adverse effects.
3. Manufacture of herbal medicines is not governed by the same strict criteria as that of conventional pharmaceuticals.
4. Good quality evidence of therapeutic or adverse effects of herbal medications is lacking, leading to reliance on anecdotal incidents and case reports.

### QUESTIONS

1. What are the readily available herbal preparations that may increase bleeding tendency?

Answer:

- Garlic: Has antiplatelet effects and may potentiate warfarin resulting in an increase in international normalized ratio.
- Ginger: Inhibits thromboxane synthetase, increasing bleeding time.
- Ginkgo: May increase bleeding in patients taking anticoagulant or antithrombotic therapy.
- Ginseng: Variable. May have antiplatelet properties, but may also reduce effectiveness of warfarin.
- Also: Arnica, feverfew, vitamin E.<sup>7</sup>

2. Which herbal products should be discontinued before surgery?

Answer: Garlic, ginseng, and Valerian root should be discontinued at least 1 week before surgery. St. John's Wort should be discontinued at least 5 days before surgery. Ephedra, ginkgo, Kava, and licorice should be discontinued at least 1 day beforehand.<sup>18</sup>

### 3. Does St. John's Wort decrease the efficacy of digoxin?

Answer: Yes. St. John's Wort is a potent inducer of the hepatic cytochrome P450 microsomal enzymes, thus increasing the metabolism of digoxin. This additionally affects levels of warfarin, theophylline, cyclosporine, anticonvulsants, and antiretrovirals.<sup>10</sup>

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# Levosimendan and Acute Heart Failure

Dorothy Breen

## CASE FORMAT: REFLECTION

A 47-year-old female presented to the emergency department with increasing shortness of breath. In the preceding week, she had woken several times during the night unable to breathe or lie flat. The patient had no history of chest pain or palpitations, was well known to the cardiology service, and had a history of ischemic cardiomyopathy. Six years previously, she had undergone coronary artery bypass graft surgery; she also had a pacemaker in situ. Her medications were furosemide 20 mg twice per day, bisoprolol 10 mg once per day, and enalapril 5 mg once per day. On examination, the patient was alert but cyanosed and in marked respiratory distress. Her respiratory rate was 35 beats per minute; pulse, 105 beats per minute, regular; and blood pressure, 130/75 mm Hg. On auscultation, crackles were audible at both lung bases. Examination of the cardiovascular system revealed an elevated jugular venous pressure, displaced apex, and a third heart sound. The emergency physician administered 60% oxygen by face mask and 60 mg of furosemide intravenously. The following tests were ordered: arterial blood gases (Table 49.1), full blood count, urea, electrolytes, glucose, creatinine, liver function tests, troponin level (Table 49.2), and an electrocardiogram. The patient's chest radiograph is shown in Figure 49.1. There was some clinical improvement, but oxygen saturation measured by pulse oximetry was 89%. It was decided to notify the intensive care team. Continuous positive airway pressure (CPAP) via face mask (positive end-expiratory pressure, 10 cm water; 60% oxygen) and an intravenous infusion of glyceryl trinitrate were commenced. In the intensive care unit, an echocardiogram was performed, and left ventricular ejection-fraction was estimated at 20%. This was a notable reduction from previous estimates. Troponin levels were not elevated, and there were no new changes on the electrocardiogram. Six hours after admission, the patient was found to be tolerating CPAP well but desaturated rapidly if the mask was removed even for brief periods. In addition, her renal function had started to deteriorate. The intensivist reviewed her and commenced dobutamine 5  $\mu$ g/kg per minute. The following day, the patient still required face mask CPAP, glyceryl trinitrate, and regular intravenous furosemide 60 mg three times daily. A different intensivist was now on duty and found the situation unchanged except that the patient's renal parameters had continued to deteriorate (Table 49.2). He decided to administer levosimendan in place of dobutamine. A bolus dose of

6 mcg/kg followed by an infusion of 0.2  $\mu$ g/kg per minute was administered. Six hours later, the patient developed rapid atrial fibrillation at 130 beats per minute. Her blood pressure remained stable, and she was treated with amiodarone. She also received potassium supplementation, as her plasma potassium concentration had decreased to 3.0 mmol/L. Over the next 24 hours, the patient's dyspnea improved significantly, but her renal function continued to deteriorate (Table 49.2).

## REVIEW

This patient presented with an episode of severe acute on chronic heart failure. Despite the frequency with which this clinical situation occurs, therapeutic options are limited, and as many as 25% of patients die within 6 months of presentation.<sup>1</sup> This patient was initially treated with oxygen, diuretics, and a peripheral vasodilator. Current guidelines emphasize these treatments as the cornerstones of therapy.<sup>2,3</sup> Loop diuretics are by far the most common agents used in this setting despite the lack of data from large clinical trials on their use.<sup>4</sup> The absence of hypotension in this case facilitated the use of a vasodilator (glyceryl trinitrate). CPAP was well tolerated and alleviated the patient's initial hypoxemia (Table 49.1).

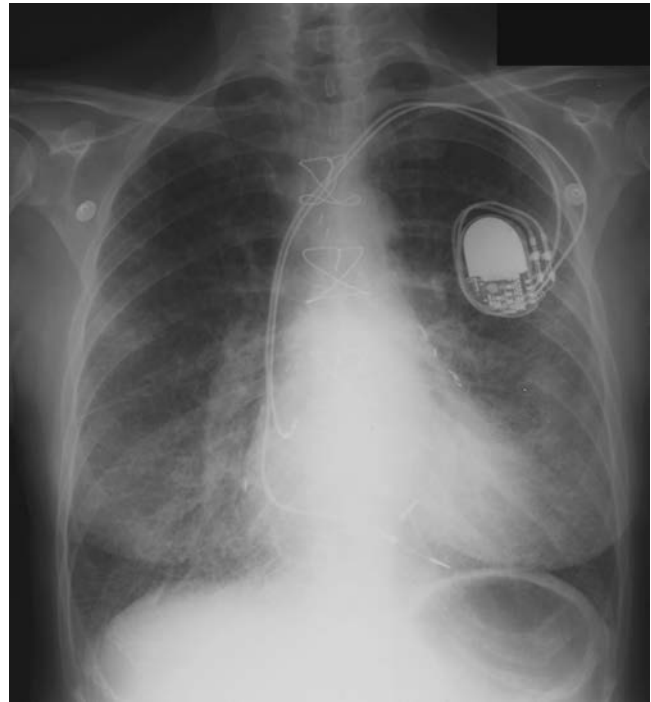
The onset of renal dysfunction is of concern. Inadequate renal blood flow caused by poor cardiac output and hypovolemia resulting from aggressive diuresis contributed in this instance (Table 49.2). Short-term inotropic support is said to be indicated when there is evidence of hypoperfusion (i.e., the onset of renal dysfunction in this case). Dobutamine was the initial agent chosen for this purpose. However, the evidence to support the use of inotropes in this setting is not clear.<sup>5,6</sup>  $\beta$ -Agonists (e.g., dobutamine) and phosphodiesterase inhibitors (e.g., milrinone) are typically chosen for their ability to inodilate. More recently, levosimendan has received attention as a novel inotrope for this purpose. Levosimendan enhances myocardial sensitivity to calcium by binding to cardiac troponin C and does so in a calcium-dependent manner. Thus, the effect is greatest at times of high intracellular calcium concentration (i.e., during systole) and least at times of low intracellular calcium concentration (i.e., during diastole). Unlike other agents, levosimendan is capable of improving contractility without increasing myocardial oxygen demand. In addition, it activates adenosine triphosphate-dependent potassium channels in vascular smooth muscle producing peripheral and coronary vasodilation. In theory, these properties make levosimendan an ideal agent for use in

**TABLE 49.1** Arterial Blood Gases Taken in the Emergency Room

	<b>FiO<sub>2</sub> 0.6 via Venturi Face Mask</b>	<b>FiO<sub>2</sub>, 0.6; PEEP, 10 cm Water via CPAP</b>
pH (7.35–7.45)	7.64	7.62
PaCO <sub>2</sub> (7.35–7.45)	31 mm Hg	33 mm Hg
PaO <sub>2</sub> (85–100 mm Hg)	55 mm Hg	85 mm Hg
Bicarbonate (22–26 mEq/L)	33 mmol/L	32 mmol/L

CPAP, continuous positive airway pressure; PEEP, positive end-expiratory pressure.

The most striking finding is hypoxemia, which corrects with the application of CPAP via face mask. Note also that alkalemia is present. The elevated bicarbonate level indicates metabolic alkalosis, but there is no evidence of respiratory compensation; in fact, the PaCO<sub>2</sub> is low. There are two acid-base processes here: metabolic alkalosis and respiratory alkalosis. The metabolic alkalosis is most likely caused by diuretic therapy, and the respiratory alkalosis is caused by tachypnea resulting from pulmonary edema.



**Figure 49.1 • The Patient's Chest Radiograph on Admission.** A pacemaker and evidence of previous sternotomy are clearly seen. The heart is enlarged. There is a diffuse bilateral infiltrate with Kerley B lines (predominantly at the right base). The appearances are consistent with pulmonary edema.

**TABLE 49.2** Biochemical Results Obtained at 0, 12, and 24 Hours After Admission

<b>Values</b>	<b>Initial</b>	<b>12 Hours</b>	<b>24 Hours</b>
Sodium (135–145 mmol/L)	130	131	133
Potassium (3.5–5.5 mmol/L)	3.1	3.5	3.0
Urea (3.0–8.0 mmol/L)	10	16	26
Creatinine (0.07–0.1 mmol/L)	0.10	0.14	0.16
Magnesium (0.7–1.0 mmol/L)	0.61	0.92	1.0
Bilirubin (μmol/L)	6		11
GGT (0–50 U/L)	15		21
ALP (32–110 U/L)	44		32
LDH (110–250 U/L)	122		118
AST (0–40 U/L)	22		23
ALT (0–40 U/L)	26		34
Glucose (4.0–7.5 mmol/L)	6.3	14.6	8.2
Troponin (0.0–0.2 ng/mL)	0.03	0.05	
BNP pg/mL	752	705	575

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; GGT, γ-glutamyl transferase; LDH, lactate dehydrogenase.

The initial presence of hyponatremia, hypokalemia, and hypomagnesemia indicate chronic loop diuretic use. At 12 hours, the electrolyte abnormalities have been corrected, but the patient's renal function has started to deteriorate. The result at 24 hours shows a disproportionate elevation in the urea: creatinine ratio (normally, 50–100:1); this most likely represents dehydration as a result of high-dose diuretic use. Hypokalemia recurs after levosimendan administration. Plasma BNP levels are elevated to those seen in congestive cardiac failure, although there is some decline with therapy.

this patient. The deteriorating renal function prompted the second intensivist to change from dobutamine to levosimendan in the patient discussed in this case.

In the setting of acute heart failure, levosimendan is the most widely studied inotrope to date. Encouraging results from initial studies have fueled enthusiasm for the drug. The RUSLAN investigators explored the safety and efficacy of levosimendan versus placebo in patients with left ventricular failure following myocardial infarction. Five hundred patients were randomized to receive either placebo or levosimendan in one of four different dosing regimens.<sup>7</sup> Levosimendan administered at 0.1 to 0.2  $\mu\text{g}/\text{kg}$  per minute had equivalent incidences of hypotension and ischemia when compared with placebo. Although not a primary end point, mortality was lower in the levosimendan group at 14 days (11.7% vs. 19.6%) and 180 days (22.6% vs. 31.4%).

The LIDO trial examined 203 patients similar to the present case (low output heart failure and documented left ventricular ejection fraction  $<0.35$ ).<sup>8</sup> Patients were randomly assigned to receive either levosimendan (24  $\mu\text{g}/\text{kg}$  bolus followed by an infusion of 0.1  $\mu\text{g}/\text{kg}$  per minute) or dobutamine (5–10  $\mu\text{g}/\text{kg}$  per minute) each for 24 hours. The primary end point of the trial was the proportion of patients showing hemodynamic improvement as measured by  $\geq 30\%$  increase in cardiac output and a  $\leq 25\%$  reduction in pulmonary capillary wedge pressure. A significantly greater proportion of patients in the levosimendan group compared with the dobutamine group (28% vs. 15%) reached this endpoint. Analysis of mortality data revealed a significantly greater mortality rate in the dobutamine group at both 31 days (8% vs. 17%) and 180 days (26% vs. 38%).

Subgroup analysis in the LIDO trial showed that the use of  $\beta$ -blockers, as in the case described, enhanced the hemodynamic effects of levosimendan but diminished those of dobutamine. Furthermore, decreases in mean potassium levels were observed in the levosimendan group over the 24 hours of the study. Despite initial supplementation, the patient's potassium levels fell with the administration of levosimendan in this case (Table 49.2).

This study and others led to the inclusion of levosimendan for use in patients with symptomatic low-output cardiac failure without hypotension in the 2004 European heart failure guidelines.<sup>2</sup> The durations of action of levosimendan and dobutamine differ. Levosimendan has an active metabolite OR-1896 that has a long half-life. The clinical hemodynamic effects of levosimendan can persist for up to 7 to 9 days after discontinuation of the drug. In this respect, the validity of comparing a 24-hour infusion of levosimendan with a 24-hour infusion of dobutamine has been questioned.<sup>9</sup>

The CASINO study was designed to enroll 600 patients with acute decompensated heart failure. Patients were randomized to receive a 24-hour infusion of levosimendan, dobutamine, or placebo.<sup>5,10,11</sup> The trial was terminated after 299 patients were enrolled because of improved outcome in the levosimendan group. Mortality at 6 months was 18% for the levosimendan group, 28.3% for the placebo group, and a remarkable 42% in the dobutamine group.

Two larger clinical trials have been designed to confirm these initial positive findings regarding the use of levosimendan. REVIVE-11 compared levosimendan with placebo in 600 patients with acute decompensated heart failure and left

ventricular impairment similar to this case (ejection fraction  $\leq 35\%$ ). Patients in the levosimendan group had better symptomatic improvement, greater decreases in plasma B-type natriuretic peptide (BNP) levels, and shorter duration of hospital stay when compared with those who received placebo.<sup>12</sup> Patients taking levosimendan showed a trend toward a greater mortality at 90 days (35 deaths in the placebo group vs. 45 in the levosimendan group). Mortality was not a primary end point of REVIVE-11, but the outcome data seem at odds with earlier smaller studies. Atrial fibrillation developed in the patient described in this case following levosimendan administration. In REVIVE 11, atrial fibrillation, hypotension, and ventricular tachycardia occurred more frequently with levosimendan than with placebo.

This patient had symptomatic improvement and a decrease in BNP levels when switched to levosimendan. To determine if this result translates into improved survival, the evidence from larger outcome studies is needed.

SURVIVE represents the largest outcome study to date of levosimendan use in patients with acute decompensated heart failure.<sup>13</sup> In this recently published randomized, double-blind, international trial, 1327 patients were assigned to receive a 24-hour infusion of either dobutamine (5–40  $\mu\text{g}/\text{kg}$  per minute) or levosimendan (bolus, 12  $\mu\text{g}/\text{kg}$  followed by an infusion 0.1–0.2  $\mu\text{g}/\text{kg}$  per minute). Despite a decrease in plasma BNP levels, there was no difference in mortality at 31 days (12% in the levosimendan group vs. 14% in the dobutamine group) or at 180 days (26% in the levosimendan group vs. 28% in the dobutamine group). It has been observed that the failure to demonstrate survival benefit in the SURVIVE study could in part be attributed to the fact that some patients had low systolic pressure and may have been in cardiogenic shock, rendering them unsuitable for treatment with levosimendan.<sup>10</sup> The patient described in this case presented with severe acute on chronic heart failure. Subgroup analysis of the SURVIVE data has shown that a trend toward a lower 31-day mortality rate was observed in those with a prior history of heart failure.

Is levosimendan a better choice than dobutamine for the patient described here? Given the available evidence to date, no clear case can be made for a better outcome with the use of one agent over another. Proponents of levosimendan can be reassured by the amount of data that exists when compared with other agents currently in use for acute heart failure.<sup>2,10</sup> Future trials should focus on subgroups that may benefit most from levosimendan. Patients such as the woman described in this case (on  $\beta$ -blocker therapy, with acute on chronic heart failure, and normotensive) represent a potential target population for such further study.

## KEY MESSAGES

1. Levosimendan is a novel inodilator, and its mode of action is mediated via myocardial sensitization to calcium.
2. Smaller studies point to the safety and efficacy of levosimendan in relieving symptoms, reducing BNP levels, and improving hemodynamic profile.
3. The largest clinical trial to date failed to show a long-term mortality benefit when compared with dobutamine.

## QUESTIONS

### 1. What is the mechanism of action of levosimendan?

Answer: Levosimendan is a positive inotrope which enhances myocardial sensitivity to calcium by binding troponin C in a calcium sensitive manner.

### 2. In patients with acute decompensated heart failure, does levosimendan confer a survival advantage compared to dobutamine?

Answer: Probably not. The best evidence (SURVIVE TRIAL) indicates similar mortality for patients who received one or other of these drugs at 31 and 180 days.

### 3. What is the duration of action of levosimendan?

Answer: Although usually administered by continuous infusion, clinical hemodynamic effects can persist for 7 to 9 days after discontinuation of the infusion due to an active metabolite with a long elimination half life.

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# Antiplatelet Agents, Low-Molecular-Weight Heparin, and Neuraxial Blockade

Leon Serfontein

## CASE FORMAT: REFLECTION

A 67-year-old, 83-kg man diagnosed with a rectal carcinoma was scheduled for an abdominoperineal resection. On initial screening, there was no evidence of metastatic disease. The patient had dyslipidemia, long-standing well-controlled hypertension, and coronary artery disease. Six months previously, he had presented to the emergency department with chest pain and was diagnosed with unstable angina for which he had undergone coronary angioplasty with stenting of two vessels. Since then, he had been angina-free and had good exercise tolerance (able to walk briskly for 20 to 30 minutes and to climb two flights of stairs without rest or shortness of breath). He had stopped smoking after his cardiac event but admitted to smoking 10 to 15 cigarettes a day for nearly 35 years prior to that.

The patient was currently taking the following medications once per day: aspirin 150 mg, atorvastatin 20 mg, diltiazem 360 mg, and esomeprazole 20 mg. He had discontinued clopidogrel 7 days previously as per the surgeon's instruction.

The patient's cardiorespiratory examination was unremarkable. His vital signs were as follows: temperature, 36.7°C; pulse rate, 76 beats per minute; blood pressure, 145/80 mm Hg; and respiratory rate, 18 breaths per minute.

The patient's electrocardiogram reading revealed sinus rhythm with no evidence of ischemia or previous infarction, and his chest radiograph was normal. An echocardiogram performed after his stenting showed mild concentric left ventricular hypertrophy, left ventricular ejection fraction of 60%, and normal valves.

The results of the patient's blood work were as follows: full blood count, normal (hemoglobin, 13.4 g/dl; platelets,  $190 \times 10^9/L$ ); electrolytes, normal; coagulation screen, normal (international normalized ratio, 0.9; activated partial thromboplastin time, 25 seconds); and cholesterol, 6.5 mmol/L.

An anesthetic plan was discussed with the patient on the evening before surgery. It was decided to place a thoracic epidural catheter for perioperative pain management before inducing general anesthesia. As the patient was anxious, diazepam 10 mg was prescribed. It was noted that enoxaparin 40 mg had been administered subcutaneously at 6:00 PM.

The patient arrived to the operating room at 8:30 on the following morning, and standard monitoring was

applied. An intravenous 16-gauge cannula was inserted in his left hand, followed by insertion of an epidural at the T9–10 interspace with the patient in the sitting position. Blood was aspirated through the epidural catheter and failed to clear on flushing or on incremental withdrawal of the catheter. The epidural catheter was reinserted at T8–9 without complications. After administration of a negative test dose (lidocaine 2% with adrenaline 1:200,000 U/mL), preoxygenation (100% oxygen tidal breathing for 3 minutes) was performed, and general anesthesia was induced. The patient received fentanyl 100 µg, propofol 160 mg, and vecuronium 8 mg intravenously. Anesthesia was maintained with sevoflurane in air:oxygen (50:50). Another 16-gauge cannula was inserted in the patient's right external jugular vein. A bolus of bupivacaine 0.25% 10 mL was administered via the epidural catheter in divided doses followed by an infusion of bupivacaine 0.125% with fentanyl 2 mcg/mL at 10 mL·hr<sup>-1</sup>. The surgical registrar inserted a urinary catheter. After infusion of the first liter of Hartmann's solution, paracetamol 2 g and diclofenac 75 mg were administered intravenously.

As surgery proceeded, "generalized ooze" was noted in the operative field. The patient's hemodynamic stability was maintained with intravenous fluids and intermittent boluses of phenylephrine (total, 400 mcg). Hartmann's solution (2500 mL), hydroxy-ethyl 6% (130:4) (500 mL), and two units of packed red blood cells were administered intraoperatively. The patient's measured total blood loss was 1400 mL.

At 12:00, the patient's trachea was extubated, and he was taken to the high-dependency unit. During the next 24 hours, he complained of abdominal pain intermittently, and bolus doses of bupivacaine 0.25% (6 mL each) were administered per epidural with good effect. The patient also complained of weakness in his legs but was reassured by the nurses that it was a normal effect of the epidural. Upon instruction from the surgical team, enoxaparin 40 mg subcutaneously was administered at 6:00 on the evening of the operative day.

At 3:00 PM on the first postoperative day, the patient complained of back pain and was unable to move his lower limbs. A magnetic resonance imaging scan was performed, which identified a large epidural hematoma extending from T7 to T11. An emergency decompressive laminectomy was performed to evacuate the hematoma. The patient recovered with a degree of residual lower body muscle weakness and sensory loss, which improved partially over the course of the subsequent 6 months.



## DISCUSSION

### Antiplatelet Agents and Neuraxial Blocks

Antiplatelet agents are commonly prescribed for primary and secondary prevention of cardiovascular disease and to decrease the incidence of acute cerebrovascular and cardiovascular events. Long-term dual therapy with aspirin and clopidogrel in this patient was indicated to maintain patency of his coronary stents.<sup>1,2</sup>

In the case described, the anesthetist and the surgical team were confronted with the need to balance the risk of increased blood loss if the antiplatelet agents were continued during the perioperative period, with that of coronary thrombosis if the drugs were stopped abruptly. In a meta-analysis of 41 studies evaluating aspirin-related bleeding risks in a wide range of surgical procedures, aspirin was found to increase the rate of bleeding complications (ranging from mild to severe) by a factor of 1.5 without an increase in surgical mortality or morbidity (with the exception of intracranial surgery and possibly transurethral prostatectomy).<sup>3</sup>

The well-established benefits of epidural anesthesia had to be weighed against the rare but potentially devastating complication of epidural hematoma.<sup>4,5</sup> This decision should be made on an individual basis, but any attempt to make an evidence-based decision is limited by the rarity of epidural hematomata. The American (American Society of Regional Anesthesia and Pain Medicine) and European guidelines summarize other evidence-based reviews and represent the collective experience of recognized experts in the field.

The elimination half-life of clopidogrel is short (4 hours), but recovery from the drug is long (7 days) because of irreversible platelet inhibition.<sup>8</sup> Neuraxial blockade is therefore contraindicated in a patient who has taken clopidogrel within seven days.<sup>7</sup> In the case of the patient described herein, neuraxial block was appropriately performed 7 days after clopidogrel had been discontinued. This interval should be extended to 14 days for ticlopidine, another thienopyridine derivative.<sup>6</sup>

Nonsteroidal anti-inflammatory drugs do not appear to add to the risks of neuraxial blockade, except when used in combination with other drugs that affect clotting mechanisms.<sup>6</sup> This patient received a low-molecular-weight heparin (LMWH) preoperatively as well as aspirin. If a nonsteroidal anti-inflammatory drug were to be administered, a cyclooxygenase-2 selective inhibitor would have been a better choice in this case because of its minimal effect on platelet function.<sup>6</sup>

### Timing of Needle Placement and Catheter Removal

It is necessary to time epidural needle placement and catheter removal relative to the timing of anticoagulant drug administration. This patient was at moderate-to-high risk for developing venous thromboembolism, making LMWH an important part of his management.<sup>9</sup>

Epidural needle insertion should be performed at least 10 to 12 hours after the preceding dose of LMWH. The same interval should be allowed to elapse from the last dose of LMWH until the epidural catheter is removed. As will be highlighted later, this step may have to be altered in patients at

greater risk of epidural hematoma. In the case of therapeutic anticoagulation with LMWH, this time period should be further extended to 24 hours.<sup>7</sup> After the removal of an epidural catheter, a minimum of 2 hours should elapse before subsequent LMWH administration.<sup>7</sup>

The previously mentioned guidelines apply to once-daily dosing of LMWH, which was applied in the patient described herein and which approximates European practice. Although the biochemistry and pharmacology of LMWHs vary, there is a lack of comparative studies. Experience in Europe indicates that the incidence of epidural hematoma associated with different LMWHs is similar.<sup>7</sup>

### Managing High-Risk Patients

The incidence of epidural hematoma is less than 1 in 150,000 epidurals and less than 1 in 220,000 spinal anesthetics.<sup>10</sup> In patients receiving a LMWH, the incidence of epidural hematoma is approximately 1 in 3000 patients undergoing continuous epidural anesthesia and 1 in 40,000 patients undergoing spinal anesthesia.<sup>11</sup> Several patient characteristics have been associated with an increased risk of developing spinal hematoma after neuraxial anesthesia (Table 50.1).<sup>12</sup> Based on these, the patient in this case was at greater risk of this particular complication. He had received nonsteroidal anti-inflammatory drugs (aspirin and diclofenac) in conjunction with other anticoagulants and a vessel puncture on catheter insertion. Ideally, the subsequent dose of LMWH should be delayed for 24 hours after the traumatic puncture.<sup>6,7</sup>

**TABLE 50.1** Risk Factors for Developing Spinal Hematoma

#### Patient Factors

Female gender

Increased age

Impaired hemostasis

Anatomic anomalies of spinal cord/vertebral column

#### Anesthetic Factors

Repeated, difficult needle/catheter placement

Traumatic (bloody) punctures

Epidural (cf. spinal) technique

#### Thromboprophylaxis Management Factors

LMWH with concomitant antiplatelet or anticoagulant administration

LMWH administration in the presence of an indwelling epidural catheter

Immediate pre-, intra-, or early postoperative LMWH administration

Twice-daily LMWH dosing

LMWH, low-molecular-weight heparin.

Modified from Horlocker TT, Wedel DJ, Benson H. Regional anesthesia in anticoagulated patients: defining the risks. *Reg Anesth Pain Med* 2003;28:172–198.

The provision of safe neuraxial anesthesia/analgesia concurrent with anticoagulation requires education of the entire patient care team. Patients at increased risk should be identified by and to the responsible clinicians and nurses. One option in this case would have been to avoid greater concentrations (>1.25%) of bupivacaine for “top-ups,” thus allowing better assessment and earlier detection of neurologic dysfunction. Magnetic resonance imaging is the diagnostic tool of choice for detecting epidural hematoma. Emergency decompressive laminectomy is the treatment of choice.<sup>13,14</sup> Overall, a less severe preoperative neurological deficit and early hematoma evacuation (within 6 hours) are associated with better neurological recovery.<sup>15,16</sup>

Newer and more effective anticoagulants are continuously being developed. Examples include the new synthetic pentasaccharide fondaparinux, and razaxaban, each of which has potent antithrombin activity and is intended for thromboprophylactic use. Because of their efficacy and longer elimination half-lives, these drugs pose additional problems for the anesthetist. Alternative anesthetic and analgesic techniques should be considered for patients considered to be at unacceptably high risk of epidural hematoma. Safer neuraxial alternatives such as spinal (cf. epidural) anesthesia or peripheral nerve blockade are among these options. In general, superficial limb blocks, the anatomical landmarks for which are well defined or easily visualized with ultrasound imaging and performed where a developing hematoma can be easily accessed and compressed, are not contraindicated in patients receiving anticoagulation.<sup>7</sup>

#### KEY MESSAGES

1. Neuraxial blockade is contraindicated in a patient who has taken clopidogrel within 7 days.
2. Epidural needle insertion as well as epidural catheter removal should be performed at least 10 to 12 hours after the preceding dose (prophylactic regimen) of LMWH.
3. Magnetic resonance imaging is the diagnostic tool of choice for detecting epidural hematoma, and emergency decompressive laminectomy is the treatment of choice.
4. A less severe preoperative neurological deficit and early hematoma evacuation (within 6 hours) are associated with better neurological recovery.

#### QUESTIONS

1. How could the risk of epidural hematoma associated with neuraxial anesthesia be minimized?

Answer:

- Identifying patients at unacceptably high risk and considering alternative anesthetic/analgesic techniques such as peripheral nerve blocks when feasible.
- Performing spinal anesthesia in preference to epidural anesthesia when possible.
- Timing needle insertion and epidural catheter removal appropriately in the presence of perioperative anticoagulation (to occur at the nadir of anticoagulant activity).

An indwelling epidural catheter should not be removed while the patient is therapeutically anticoagulated.

- Avoiding combinations of drugs (perioperatively) that independently alter coagulation.
2. What are the symptoms of cord compression from an epidural hematoma?
  3. Following removal of an indwelling epidural catheter, how long is the wait before the next dose of prophylactic heparin could be safely administered?

Answer: Symptoms include severe back pain, new-onset, or persisting sensory or motor deficit outlasting the expected duration of the neuraxial block and bowel or bladder dysfunction within the postoperative period.

Answer: A minimum of 2 hours.

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# Neuroprotection During Cerebral Aneurysm Surgery

Peter John Lee

## CASE FORMAT: REFLECTION

A 54-year-old, 65-kg woman presented to the emergency department with sudden-onset severe headache, vomiting, and drowsiness. Her Glasgow Coma Scale score was 13. Computed axial tomography showed diffuse subarachnoid hemorrhage (SAH) from an aneurysm. Four-vessel cerebral angiography was performed and revealed a ruptured aneurysm on the anterior communicating artery. Nimodipine 60 mg was administered to the patient orally, and phenytoin 975 mg was administered intravenously over 20 minutes. The patient was scheduled to undergo aneurysm clipping on the following morning.

The patient had a 10-year history of hypertension for which she took indapamide 2.5 mg and atenolol 25 mg each morning. She denied symptoms of cardiac disease but admitted to smoking 20 cigarettes each day for 20 years. The patient denied cocaine use.

On arrival to the operating room, the patient's GCS score had deteriorated to 11. Her blood pressure was 140/90 mm Hg, and her heart rate was 85 beats per minute. She had no focal neurological deficit.

The results of a full blood picture, urea, electrolytes, and blood glucose performed in the emergency department were all normal. Electrocardiograph and chest radiograph readings were unremarkable. Two units of cross-matched blood were made available.

Standard monitoring was commenced in the operating room, and a 16-gauge intravenous (IV) cannula was inserted (an 18-gauge IV cannula was already in situ). A cannula was placed in the patient's left radial artery for arterial pressure monitoring. Fentanyl 150 µg IV was administered. Anesthesia was induced with propofol 150 mg, and muscle relaxation was achieved with vecuronium 8 mg. Following tracheal intubation, anesthesia was maintained with inhaled sevoflurane at one minimum alveolar concentration in an air/oxygen mixture. A nasopharyngeal temperature probe was inserted, and a forced-air cooling blanket was placed on the patient, with the temperature set to 32°C. Immediately before pinning the patient's head in a Mayfield surgical frame, fentanyl 200 µg was administered IV, and her scalp was infiltrated with bupivacaine 0.5% 5 mL.

After incision of the dura and when optimal exposure was obtained, the surgeon announced his intention to place a temporary clip on the A1 segment of the anterior communicating artery.

Shortly after administration of thiopentone 250 mg IV, the patient's blood pressure decreased to 80/45 mm Hg. The nasopharyngeal temperature was 35.1° C. Arterial blood gas, electrolyte, and glucose analysis were performed as shown here:

pH	7.37	Na <sup>+</sup>	140 mmol/L <sup>-1</sup>
pCO <sub>2</sub>	6.3 kPa	K <sup>+</sup>	5.1 mmol/L <sup>-1</sup>
pO <sub>2</sub>	11.3 kPa	Cl <sup>-</sup>	100 mmol/L <sup>-1</sup>
HCO <sub>3</sub> <sup>-</sup>	25 mmol/L	Glucose	12 mmol/L <sup>-1</sup>
BE	0 mmol/L		
SaO <sub>2</sub>	96%		

After placement of the temporary clip, IV phenylephrine boluses of 50 µg were administered as required to maintain the patient's blood pressure within a mean arterial pressure of 70 to 80 mm Hg. Ninety minutes later, after placing the permanent clip on the aneurysm, the surgeon removed the temporary clip. The total surgical blood loss was approximately 200 mL and was replaced with 250 mL colloid. Normal saline 2000 mL was administered over the course of the operation. The surgery lasted for 150 minutes.

During surgical closure, the cooling blanket temperature setting was increased to 38°C. Fentanyl 200 µg was administered at this time. The inspired concentration of inhalational agent was decreased, and reversal of neuromuscular block was achieved using glycopyrrolate 500 µg and neostigmine 2.5 mg. The patient's trachea was extubated when she demonstrated a satisfactory spontaneous ventilatory pattern and nasopharyngeal temperature was 37°C. Twenty minutes after discontinuing the inhalational agent, the patient had emerged sufficiently to obey commands. She did not cough with extubation, and her blood pressure was 135/92 mm Hg at the time.

The patient was transferred to the postanesthesia care unit where she was noted to be drowsy but rousable with a Glasgow Coma Scale score of 14. She had no focal neurological deficit. Morphine was administered intravenously to a total of 8 mg, titrated to patient request, and she was transferred to the high-dependency unit for continued monitoring.

Cerebral angiography 2 weeks after surgery showed obliteration of the aneurysm and no additional aneurysms. The patient was maintained on nimodipine for 21 days after surgery and was discharged home having made a full neurological recovery.

## CASE DISCUSSION

Cerebral aneurysms have a prevalence of 0.2% to 9.9% in the general population.<sup>1</sup> The incidence of SAH resulting from ruptured cerebral aneurysms ranges from 6 to 16 per 100,000, depending on the population under study.<sup>2,3</sup> In the United States, this figure accounts for 25,000 to 30,000 cases of SAH per year.<sup>4</sup>

The application of temporary clips to a cerebral artery during surgical exploration and repair of an intracranial aneurysm is performed when the risk of rupture is high. Temporary clipping causes a period of focal cerebral ischemia and the anesthetist should institute measures for neuroprotection in this situation.

### Neuroprotection

Neuroprotective strategies are intended to modify intracellular and vascular biological responses to deprivation of the cellular energy supply to increase tissue tolerance to ischemia and/or reperfusion resulting in improved outcome.<sup>5</sup> Uncontrolled release of glutamate during ischemia and the consequent excessive stimulation of postsynaptic receptors are implicated in the initiation of neuronal injury, a process known as *excitotoxicity*. Neuronal apoptosis occurs early during ischemia and is responsible for some of the continued neuronal loss that is seen following the insult.

### Blood Pressure

Maintaining a high normal cerebral perfusion pressure (CPP) can augment collateral blood flow to the ischemic penumbra, minimize secondary injury, and result in improved neurological outcome. This is particularly germane when a temporary clip has been applied, and collateral perfusion to affected areas can occur through Willisian channels, pial-to-pial collaterals, or leptomeningeal pathways. CPP should be maintained at a greater level in patients who are chronically hypertensive and whose autoregulatory curves are shifted to the right. It may be best to maintain the blood pressure of such individuals close to their pre-SAH measurements. In this case, the anesthetist maintained the mean arterial pressure between 70 to 80 mm Hg; in the absence of accurate data on the patient's baseline blood pressure, this is acceptable management.

### Partial Pressure of Carbon Dioxide

During periods of focal cerebral ischemia, ventilation should be altered to ensure normocapnia. Hypercapnia can cause intracerebral "steal" by preferentially vasodilating vessels in the noninjured area and decreasing intracellular pH. Hypocapnia does not cause the putative inverse-steal phenomenon and can increase the size of the region at risk of ischemic damage. The hypercapnia seen in the arterial blood gas analysis in this case (pCO<sub>2</sub>, 6.3 kPa) should have been corrected promptly.

### Blood Glucose

Hyperglycemia increases damage in focal ischemia and is an independent predictor of poor outcome in patients who have focal ischemic injury. During incomplete ischemia, glucose is metabolized anaerobically by glycolysis, with a resultant

accumulation of lactic acid and decrease in pH. The buffering capacity of the brain is exceeded, and reactive oxygen species are generated leading to cell membrane rupture and neuronal necrosis. The hyperglycemia noted in this patient should have been corrected.

In clinical practice, it is advisable to avoid glucose-containing solutions and to correct hyperglycemia aggressively (target concentration, 5–9 mmol/L<sup>-1</sup>) in patients with focal cerebral ischemia.

### Temperature

Hypothermia can offer some degree of neuroprotection in focal and global ischemia. Early studies have shown that hypothermia decreases cerebral metabolic rate (CMR) in a temperature-dependent fashion, with the greatest effect at very low temperatures (18°C–22°C) achievable only with cardiopulmonary bypass. The effects of mild hypothermia (cooling to 32°C–35°C) were found to be negligible. Reduction in brain temperature by 2°C to 4°C has been shown to be neuroprotective in rats. The protective effects of hypothermia are more likely to be dependent on changes at several steps in the ischemic cascade than on change in CMR alone. Possible mechanisms include suppression of glutamate release and decrease in nitric oxide production leading to a reduction in free radical-triggered lipid peroxidation. Disappointingly, a prospective trial has shown that short-duration intraoperative hypothermia (33°C) did not improve 3-month neurologic outcome after craniotomy for good-grade patients with aneurysmal subarachnoid hemorrhage.<sup>6</sup>

Hypothermia causes shivering with increased oxygen demand, is associated with arrhythmias and cardiac ischemia, decreased platelet activity, disordered coagulation, and increased infection rate.

The conflicting nature of such study results as well as the paucity of prospective trials in the area leave many anesthetists unsure of hypothermia's role in neuroprotection. The mild hypothermia achieved in the patient discussed in this case would have provided little neuroprotection and may have contributed to the delay in emergence. A timely emergence is important so that prompt neurologic examination can be performed.

Without doubt, hyperthermia has adverse effects on the postischemic brain. Spontaneous hyperthermia, common in the postischemic brain, is associated with poor outcome in humans and should be treated aggressively.<sup>7</sup>

## IV Anesthetic Agents

The protective effect of barbiturates in focal cerebral ischemia has been shown in one human trial and in numerous animal trials.

This effect is thought to be caused by suppression of the CMR, which produces a progressive decrease in electroencephalographic activity and a reduction in the rate of adenosine 5-triphosphate depletion. It may also result from cerebral blood flow (CBF) redistribution to peri-ischemic areas, free radical scavenging, and potentiation of  $\gamma$ -aminobutyric acid activity.

The potential for barbiturates to confer long-term neuroprotection has not been investigated.

Propofol may have beneficial effects on cerebral physiology. It decreases CMR and CBF. It can also protect the brain against ischemic injury in rats. Neuroprotection by propofol

might result from a direct scavenging effect on reactive oxygen species generated during ischemia and reperfusion.<sup>8</sup> Propofol, compared with nitrous oxide and fentanyl, decreases neuronal injury and favorably modulates apoptosis-regulating proteins for at least 28 days. This suggests that propofol could be neuroprotective over a long postischemic period, particularly if the insult is mild.<sup>9</sup> Because propofol has negative inotropic and vasodilatory properties, it may decrease CPP if a large dose is administered rapidly.

Ketamine increases intracranial pressure, CMR, and CBF. However, it also inhibits glutamatergic neurotransmission at the N-methyl-D-aspartate receptor, which is highly activated by the excitatory transmitter release that occurs during ischemia. There are no human data supporting the use of ketamine in brain protection.

Lidocaine blocks apoptotic cell death *in vitro*, and, in antiarrhythmic doses, it decreases infarct size and improves neurologic outcome in a rat model of transient ischemia.<sup>10</sup> Opioids (such as fentanyl, used in this case) are useful adjuncts as they limit the need for higher-dose volatile anesthetics with attendant cerebral vasodilation and increased CBF. Evidence as to whether opioids produce neuroprotection is lacking. The short half-life of fentanyl in moderate doses allows timely postsurgical neurological evaluation.

The use of thiopentone in this patient was appropriate. Propofol can also be used as a neuroprotective agent and can circumvent the delayed emergence seen with large doses of barbiturates.

## Inhalational Anesthetic Agents

Inhalational anesthetic agents can decrease ischemic cerebral injury. Both halothane and sevoflurane reduce the volume of infarction after focal ischemia.<sup>11</sup> This occurs because these agents attenuate excitotoxicity by inhibiting glutamate release and postsynaptic glutamate receptor-mediated responses. The neuroprotection offered by isoflurane, and possibly other inhalational agents, appears to be short-lived; a reduction in neurologic injury is seen when evaluated at 2 days but not 14 days after ischemic injury.<sup>12</sup>

Like the barbiturates, most inhalational anesthetic agents produce progressive electroencephalographic depression in a dose-dependent manner, with a similar reduction in CMR.

Halothane is a potent cerebral vasodilator that can produce a marked increase in intracranial pressure. Hyperventilation can be used to prevent this increase but must be instituted before introducing the halothane, as the vasodilatory effects occur faster than the onset of metabolic suppression. Enflurane is a less potent cerebral vasodilator and more potent depressant of CMR. Greater doses of enflurane produce cerebral seizure activity when combined with hypocarbia. Isoflurane is the least potent cerebral vasodilator and most effectively decreases CMR. Greater intracranial pressure increases with its use, hyperventilation minimizes the effect and can be safely instituted after introduction of the agent. Desflurane and sevoflurane have similar properties to isoflurane. The lower blood-gas solubility of desflurane and sevoflurane allow more prompt awakening.

Interestingly, sevoflurane has been shown to provide longer-term protection in an experimental model of focal cerebral ischemia. The use of sevoflurane in the patient presented in this case was appropriate.

## “Triple-H” Therapy

Vasospasm after surgery is a major cause of morbidity and mortality following SAH. Constriction of the cerebral arterial vasculature occurs as free subarachnoid blood under high pressure comes into contact with the surfaces of vessels, particularly in the basal cisterns. The mainstay of medical treatment of cerebral vasospasm, in addition to calcium channel blockade with nimodipine, is “triple-H” therapy: hypervolemia (an increase in the volume of circulating plasma), induced arterial hypertension, and hemodilution. Postoperative “triple-H” therapy has been used in many centers, on the basis that it augments CBF, prevents delayed ischemia, and improves clinical outcome. However, the efficacy of “triple-H” therapy has not been proven by prospective study.<sup>13</sup> Although induced hypertension results in a significant increase in regional CBF and brain tissue oxygenation, hypervolemia/hemodilution induce only a slight increase in regional CBF, while brain tissue oxygenation does not improve<sup>14</sup> (Table 51.1).

### KEY MESSAGES

1. Maintaining a high normal CPP can augment collateral blood flow to the ischemic penumbra, minimize secondary injury, and result in improved neurological outcome.
2. Hyperglycemia increases damage in focal neurologic ischemia and is an independent predictor of poor outcome in patients who have focal ischemic injury.
3. Hyperthermia has adverse effects on the postischemic brain.
4. The efficacy of “triple-H” therapy (hypervolemia – [an increase in the volume of circulating plasma], induced arterial hypertension, and hemodilution) has not been proven by prospective study.

### QUESTIONS

#### 1. What is neuroprotection?

Answer: Neuroprotection is modification of intrasystemic cellular and vascular biological responses to deprivation of the cellular energy supply to increase tissue tolerance to ischemia and/or reperfusion resulting in improved outcome.

#### 2. What is the best ventilatory strategy to use during general anesthesia for cerebral aneurysm repair?

Answer: Ventilation should be carried out to achieve normocapnia. Hypercapnia can cause intracerebral “steal” by preferentially vasodilating vessels in the noninjured area and decrease intracellular pH. Hypocapnia can increase the size of the region at risk of ischemic damage.

#### 3. What inhalational agents are suitable for use in a case in which neuroprotection is desirable?

Answer: Desflurane and sevoflurane are suitable for use in a case in which neuroprotection is desirable. Both of these agents offer some neuroprotection with easy control

**TABLE 51.1** Evidence-Based Status of Plausible Interventions to Reduce Perioperative Ischemic Brain Injury

Intervention	Pre-ischemic Efficacy in Experimental Animals	Post-ischemic Efficacy in Experimental Animals	Pre-ischemic Efficacy in Humans	Post-ischemic Efficacy in Humans	Sustained protection in experimental animals	Sustained protection in humans
Moderate hypothermia	++	++	-/+	++*	++	++
Mild hyperthermia	---	---	--	--	---	--
Hyperventilation	--	--	--	--	--	--
Normoglycemia	++	--	+	+	++	--
Hyperbaric oxygen	++	--	--	-/+	--	--
Barbiturates	++	-	+	-	--	--
Propofol	++	+	-	--	--	-
Etomidate	---	--	--	--	--	--
Nitrous oxide	-	--	--	--	--	--
Isoflurane	++	--	--	--	++	--
Sevoflurane		--	--	--	++	--
Desflurane	++	--	--	--	--	--
Lidocaine	++	--	+	--	--	--
Ketamine	++	--	--	--	--	--
Glucocorticoids	---	--	--	--	--	--

++, repeated physiologically controlled studies in animals/randomized, prospective, adequately powered clinical trials; +, consistent suggestion by case series/retrospective or prospective small sample size trials, or data extrapolated from other paradigms; -/+, inconsistent findings in clinical trials; may be dependent on characteristics of insult; -, well-defined absence of benefit; --, absence of evidence in physiologically controlled studies in animals/randomized, prospective, adequately powered clinical trials; ---, evidence of potential harm; \*, out-of-hospital ventricular fibrillation cardiac arrest. Reproduced with permission from Fukuda S, Warner DS. Cerebral protection. *Br J Anaesth* 2007; 99:10–17.

of vasodilation. The low blood-gas solubility of these agents allows prompt awakening.

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# Anesthesia for Cerebral Aneurysm Coiling

Ashit Bardhan

## CASE FORMAT: REFLECTION

A 65-year-old, 75-kg male was admitted to the emergency department with a severe headache and decreased level of consciousness. His Glasgow Coma Scale score was 14. A computed tomographic scan showed subarachnoid hemorrhage (SAH). An angiogram demonstrated (Fig. 52.1) that the source of the SAH was an 8-mm posterior communicating artery aneurysm.

The patient had smoked 3 to 5 cigarettes per day for the previous 30 years. He walked 2 kilometers each day on level ground and denied chest pain or dyspnea on exertion. He had undergone an appendectomy at 16 years of age for which the anesthetic had been uneventful.

The patient's neurologic examination revealed a Glasgow Coma scale of 14 (Table 52.1); he opened his eyes in response to voice (3), was oriented and conversing (5), and obeyed commands (6). He was judged to be Hunt and Hess grade II (Table 52.2) and also grade II by World Federation of Neurological Surgeons Grading (Table 52.3). His pupils were 6 to 7 mm in diameter, were equal, and reacted normally to light. He had no neurologic deficit. Electrocardiogram (ECG) and chest radiograph readings were unremarkable. The patient's serum urea was 6.5 mmol/L; creatinine, 85 mmol/L; sodium, 130 mmol/L; and glucose, 8.5 mmol/L. His hemoglobin concentration was 14.6 g/dL, and his white blood cell count was  $12 \times 10^9/L$ .

The patient had been fasting for 6 hours and had received 60 mg of oral nimodipine (additional doses had been prescribed every 4 hours thereafter). A prophylactic dose of phenytoin 1.125 g (15 mg/kg) had been administered intravenously on admission over 30 minutes in the emergency department.

In view of the hyponatremia, the patient's estimated fluid losses were replaced with 0.9% sodium chloride. As part of the multidisciplinary approach to managing a cerebral aneurysm, the neurosurgeon and neuroradiologist discussed definitive treatment options such as clipping and coiling of the aneurysm. On the basis of findings of the International Subarachnoid Aneurysm Trial (ISAT)<sup>1</sup> trial, they decided to proceed to coiling of the aneurysm on the following day.

On the next morning, the patient received the prescribed dose of nimodipine. He received no premedicant, as he volunteered that it was not necessary. In the neuroradiology suite, standard monitors (ECG, SpO<sub>2</sub>, and noninvasive

blood pressure) were applied. One 16-gauge cannula was inserted on the dorsum of the patient's left hand after 1% lignocaine infiltration at the site. A 20-gauge arterial cannula was inserted in the left radial artery for invasive monitoring of blood pressure also after local infiltration with 1% lignocaine. After 3 minutes of preoxygenation with 100% oxygen, anesthesia was induced using intravenous propofol 200 mg and fentanyl 150. Muscle relaxation was achieved with intravenous atracurium 40 mg. Anesthesia was maintained using an infusion of propofol (target control infusion targeted plasma concentration was 4 ng/L) and remifentanyl (target control infusion, 6–9 ng/L). Bispectral index monitoring was commenced and maintained <60 by titrating the propofol infusion. Convected warm air was circulated on the patient's body (Bair Hugger; Arizant Inc, Eden Prairie, MN), for which the temperature was set at 38°C. Once the right femoral artery was successfully cannulated, 100 IU/kg of heparin was administered. Three minutes later, the activated clotting time was 345 seconds. Using a microcatheter, the neuroradiologist catheterized the aneurysm and then successfully deposited platinum coils within the aneurysm sac until it was occluded. Propofol and remifentanyl infusion were discontinued. Reversal of neuromuscular block was achieved by administering 2.5 mg neostigmine and 500 µg glycopyrrolate. During the procedure, 1 L of 0.9% sodium chloride had been administered. Within 12 minutes of discontinuing the anesthetic agents, the patient was able to obey commands, and his trachea was extubated without coughing. He was transferred to the postanesthesia care unit, and after 30 minutes, he was oriented, alert, awake, and comfortable. His vital signs were normal and he was discharged to the neurosurgical observation ward. Regular nimodipine and phenytoin were prescribed for 3 weeks, and the patient was scheduled for a repeat cerebral angiogram in 6 months.

## CASE DISCUSSION

### ISAT

The ISAT is the only large-scale, multicenter, prospective, randomized control trial that has compared endovascular coiling and neurosurgical clipping for ruptured intra-cerebral aneurysm. A total of 2143 patients were randomly allocated, 1073 to the endovascular and 1070 to the neurosurgical arms. The trial included patients with ruptured aneurysms that

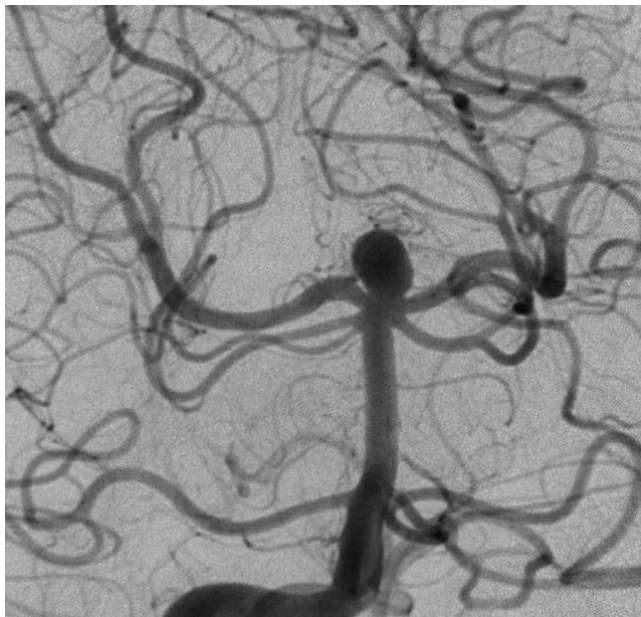


Figure 52.1 • Precoilng Angiogram.

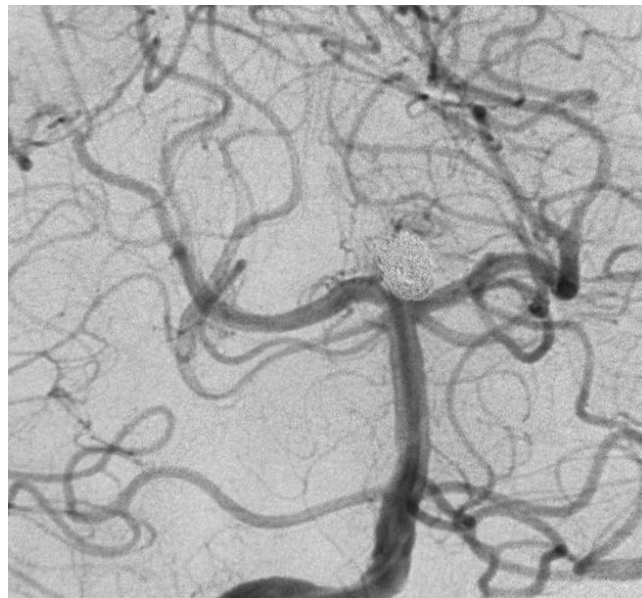


Figure 52.2 • Postcoiling Angiogram.

TABLE 52.1 Glasgow Coma Scale

Score	6	5	4	3	2	1
Eyes	N/A	N/A	Opens eyes spontaneously	Opens eyes in response to voice	Opens eyes in response to painful stimuli	Does not open eyes
Verbal	N/A	Oriented, converses normally	Confused, disoriented	Utters inappropriate words	Incomprehensible sounds	Makes no sounds
Motor	Obeys commands	Localizes painful stimuli	Flexion / withdrawal to painful stimuli	Abnormal flexion to painful stimuli	Extension to painful stimuli	Makes no movements

N/A, not applicable.

TABLE 52.2 Hunt and Hess Grading Scale for Subarachnoid Hemorrhage

Grade	Clinical Description
I	Asymptomatic or minimal headache and slight nuchal rigidity
II	Moderate- to- severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy
III	Drowsiness, confusion, or mild focal deficit
IV	Stupor, moderate- to- severe hemiparesis, and possibly early decerebrate rigidity and vegetative disturbance
V	Deep coma, decerebrate rigidity, and moribund appearance

TABLE 52.3 World Federation of Neurological Surgeons Grading Scheme for Subarachnoid Hemorrhage

Grade	Glasgow Coma Scale	Motor Deficit
I	15	Absent
II	13 or 14	Absent
III	13 or 14	Present
IV	7–12	–
V	3–6	–



were amenable to treatment with clipping or coiling. Patients randomly allocated to coiling experienced a 23.7% incidence of neurological dependency or death compared with a 30.6% incidence in patients randomized to clipping. These results showed that the absolute benefit of coiling over clipping was 7.4%. This figure equates to a number needed to treat of 14 patients, for one to avoid death or dependency at 1 year after rupture.

Several aspects of this study need to be emphasized to place the findings into proper clinical perspective. Only 22.4% of the initially screened 9559 patients with ruptured aneurysms underwent randomization; <10% of the patients were at high clinical risk, and approximately 95% of them had aneurysms in the anterior cerebral circulation with a size of <10 mm. Complete occlusion of the aneurysm was achieved more often in the surgically treated group compared with the endovascularly treated group (82 vs. 66%). Late aneurysm rebleeding was more common in the coiled group (0.2% per year) than in the open surgical group (0.06% per year); however, rebleeding was uncommon in both treatment groups and did not reverse the benefit of endovascular treatment at 7-year follow-up.<sup>2</sup>

### **What is coiling of a cerebral aneurysm?**

Coiling is a procedure in which a microcatheter is inserted through the femoral artery, navigated into the aneurysm sac allowing detachable coils to be advanced into the sac until the aneurysm is occluded. The original coils are named Guglielmi Detachable Coils after Dr. Guido Guglielmi, the developer of the technique.

### **What are the advantages of coiling?**

Coiling is a minimally invasive procedure. It also avoids the complications associated with craniotomy. Recovery time is shorter than after clipping. Within the setting described of the ISAT trial, coiling was associated with a better outcome (in terms of neurologic dependency or death) than surgical clipping.

### **How is the decision made to coil a cerebral aneurysm?**

Several factors are important in deciding if an aneurysm is suitable for coiling. The following factors favor coiling: small aneurysm sac size (but not too small, >3 mm), favorable neck size (not wide), no branches coming out of the dome of the aneurysm, certain locations where surgical access is difficult (basilar artery, parophthalmic artery), advanced age, and severe systemic disease. Approximately 7 out of 10 ruptured aneurysms are suitable for coiling. In many cases, aneurysms can be secured using either technique.

### **What is the optimal timing for intervention?**

Cerebral vasospasm usually develops 3 to 12 days after SAH, lasts on average 2 weeks, and affects 60% to 70% of patients with SAH. It frequently results in cerebral ischaemia, and is the major cause of morbidity and mortality in these patients. After SAH has been diagnosed, it should be repaired at the earliest possible time before cerebral vasospasm develops.

### **What is the role of nimodipine?**

Nimodipine, a calcium channel blocker, improves outcome after SAH.<sup>3</sup> Nimodipine therapy (60 mg orally or by nasogastric tube every 4 hours; maximal daily dose 360 mg) should be started in all patients at admission and continued for 21 days. Nimodipine administered as a continuous infusion is no more effective than when administered orally, but it is associated with a greater incidence of hypotension. Intravenous nimodipine should be administered via a central venous catheter. In addition, the infusion system must be protected from light. If an adequate and stable blood pressure (systolic blood pressure 130–150 mm Hg) cannot be maintained, hemodynamic management takes priority over nimodipine administration. In general, nimodipine renders patients prone to hypotension, especially when they are intravascularly depleted and during anesthesia induction. As nimodipine does not reliably relieve angiographically documented vasospasm, its beneficial effect may be caused by a general brain protective mechanism.<sup>2</sup>

### **How is grading and neurologic assessment used?**

Clinical grading scales such as that of Hunt and Hess<sup>4</sup> or the World Federation of Neurological Surgeons<sup>3</sup> are used to standardize clinical assessment and to estimate patients' prognosis. Focal neurologic deficits and change in mental status are the basis of the Hunt and Hess grading scale, which has been used as a predictor of outcome. A frequently overlooked part in this classification is that, if patients have medical comorbidities, such as hypertension, severe atherosclerotic disease, chronic pulmonary disease, diabetes mellitus, and severe vasospasm, the grade should be the next less favorable one. The World Federation of Neurosurgical Societies has introduced a new grading system that has more accurate prognostic value and is partially based on the Glasgow Coma Scale of patients on arrival.<sup>5</sup> Knowledge and understanding of the grading scales are required for effective communication among physicians, assessment of the severity of the patient's underlying pathophysiological abnormalities, and rational planning of the perioperative anesthetic management.<sup>2</sup>

### **What type of electrolyte abnormalities may occur?**

Common electrolyte abnormalities include hyponatremia, hypokalemia, hypomagnesemia, and hypocalcemia. Hypomagnesemia occurs in more than 50% of patients with SAH and is associated with delayed cerebral ischemia and poor outcome.<sup>6,7</sup> If hyponatremia is caused by the syndrome of inappropriate anti-diuretic hormone secretion, normovolemia should be maintained with isotonic saline.<sup>8</sup>

### **Which type of anesthetic technique is generally used to facilitate coiling?**

Conscious sedation, "neurolept" anesthesia, and general anesthesia have been described. Anesthetists in most hospitals use general anesthesia with tracheal intubation.<sup>7</sup> Airway management using a laryngeal mask airway has also been advocated.

**What types of premedication are used?**

If the patient is alert and very anxious, an anxiolytic can be prescribed.<sup>8</sup> A small dose of benzodiazepine is usually sufficient. On the other hand, in cases of altered consciousness, sedative premedication should be avoided. Opiates are best avoided, as they can cause respiratory depression. The patient might already be taking a calcium channel antagonist such as nimodipine as a neuroprotective agent or for decreasing the incidence of vasospasm. Anticonvulsants, corticosteroids, and antibiotics might be used as premedicants depending on the patient's status and requirements. In patients with obesity or gastroesophageal reflux, H<sub>2</sub>-receptor antagonists such as ranitidine or metoclopramide are used to decrease the risk of pulmonary aspiration of gastric contents.<sup>9</sup>

**What type of electrocardiographic changes take place?**

SAH can be associated with marked systemic and pulmonary hypertension, cardiac arrhythmias, myocardial dysfunction and injury, and neurogenic pulmonary edema. ECG abnormalities (e.g., QT<sub>c</sub> prolongation, repolarization abnormalities) have been reported in 25% to 100% of cases, along with an increase in serum concentration of cardiac troponin in 17% to 28%, of creatine kinase-MB isoenzyme in 37%, and of left ventricular dysfunction in 8% to 30% of cases. In most cases, myocardial dysfunction seems to correlate more with the degree of neurologic deficit than with the severity of ECG abnormalities.<sup>2</sup> Cardiac injury and dysfunction usually resolve over time and do not seem to directly affect morbidity and mortality.<sup>10</sup>

**What type of monitoring is used?**

Monitoring standards in a neuroradiology interventional suite should be equivalent to those available in the operating room. Invasive blood pressure monitoring and urine output measurement are required. A central venous catheter is not regularly inserted, as large fluid shifts are not expected. Neurophysiologic monitoring is used in some hospitals but is not a common practice.

**What are the principles of anesthetic management?**

The goal during anesthesia induction for repair of cerebral aneurysms is to minimize the risk of aneurysm rupture. The incidence of aneurysm rupture during induction is approximately 2%.<sup>11</sup> As there is no skull decompression during the procedure, the risk of aneurysm rupture is present until it is coiled successfully. Anesthesia is maintained by total intravenous anesthesia or a combination of low-dose propofol and remifentanyl in conjunction with small dose of a volatile agent. Cannulation of the femoral artery is associated with greatest stimulation. Overall, the anesthetic requirement is not great. Systemic hypotension should be avoided, and "low-normocapnia" should be maintained. During emergence, if the aneurysm is secured, a systolic blood pressure of 160 mm Hg has been reported to result in a favorable outcome. The safe upper limit for an unsecured aneurysm is not clear.<sup>7</sup>

**What type of complications are possible?**

Non-central nervous system complications include contrast allergic reactions, contrast nephropathy, and groin or retroperitoneal hematomata. Central nervous system complications can be categorized based on the timing of the procedure: intraprocedural, early, and late postprocedural. Intraprocedural complications include rebleed from aneurysm rupture or ischemic stroke caused by vessel occlusion (from thrombosis, embolization, branch occlusion, or dissection). Early postprocedural complications include rebleeding and delayed thromboembolism. The main late postprocedural complication is aneurysm regrowth (from coil compaction or aneurysm growth).

**CONCLUSION**

Anesthesia for coiling of cerebral aneurysms requires a thorough understanding of the pathophysiology of SAH. Anesthesia is provided in a setting with which the anesthetist may not be familiar; often, trained assistance is not readily available, and there is the potential for catastrophic complications such as re-bleeding or perforation.

**KEY MESSAGES**

With respect to the anesthetic care of patients undergoing coiling of cerebral aneurysms:

1. It is necessary for the anesthetist to familiarize him/herself with the neuroradiology suite before undertaking care of such patients.
2. Thorough neurologic assessment of the patient is required pre- and postoperatively.
3. Maintaining hemodynamic stability throughout the procedure is important to avoid the risk of secondary injury caused by hypoperfusion or aneurysm rupture.
4. Communication between the anesthetist and the interventional team is important.

**QUESTIONS**

1. What is the principal finding of the ISAT trial?

Answer: The principal finding of the ISAT trial is that patients randomly allocated to coiling experienced a 23.7% incidence of neurologic dependency or death compared with a 30.6% incidence in patients randomized to clipping.

2. What nimodipine regimen is indicated in patients with SAH?

Answer: Nimodipine (60 mg orally or by nasogastric tube every 4 hours; maximal daily dose, 360 mg) should be

administered to all SAH patients at admission and continued for 21 days.

**3. What electrolyte abnormalities are most commonly associated with SAH?**

Answer: Common electrolyte abnormalities associated with SAH include hyponatremia, hypokalemia, hypomagnesemia, and hypocalcemia.

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# Emergency Reversal of Rocuronium-Induced Neuromuscular Blockade Using Sugammadex

Mohan Mugawar

## CASE FORMAT: REFLECTION

A 38-year-old female (American Society of Anesthesiologists physical status I) presented with radicular low back pain of 3 months' duration. After appropriate investigations and discussion of the treatment options with her, she was scheduled for elective lumbar laminectomy. The patient's medical history was unremarkable. She had undergone uneventful general endotracheal anesthesia for a tonsillectomy at 5 years of age and spinal anesthesia for an elective caesarean section 2 years previously.

The preoperative evaluation revealed a moderately obese woman who was 165 cm in height and weighed 85 kg. Cardiorespiratory assessment was normal. Preoperative laboratory data were within the normal ranges. The airway assessment revealed prominent upper incisors, interincisor gap >3 cm, thyromental distance 8 cm, and Mallampati grade II. The patient's neck appeared short; the cervical spine mobility was normal. In the operating room, an intravenous (IV) cannula was inserted, and an infusion of compound sodium lactate commenced. Routine standard monitoring was applied including neuromuscular monitoring using train-of-four stimulation (TOF watch).

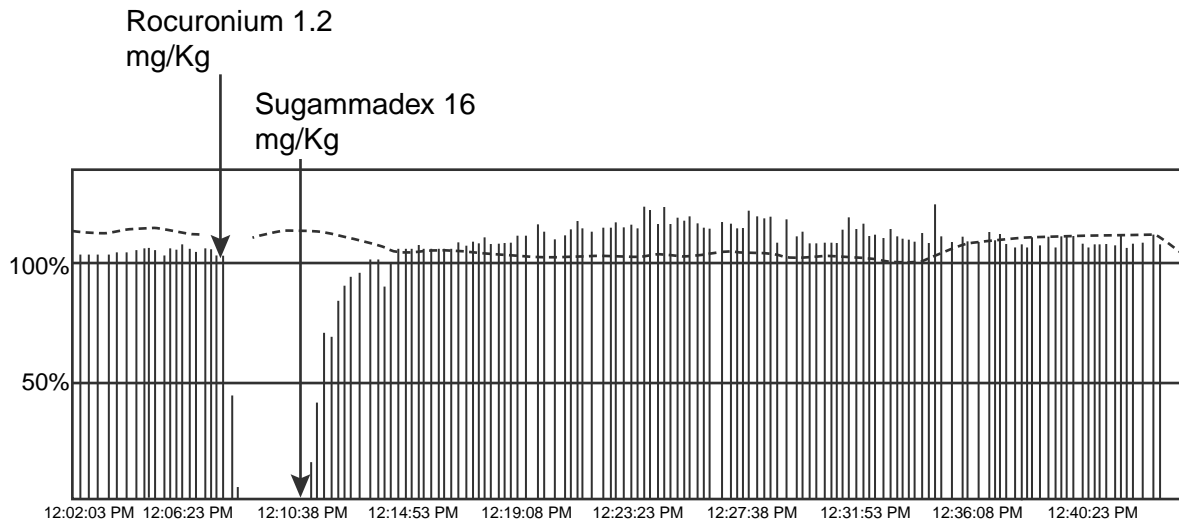
After 3 minutes of preoxygenation, anesthesia was induced by an experienced anesthesiologist with fentanyl 100 µg and propofol 200 mg. With some difficulty, positive pressure was applied via face mask, and some chest expansion was noted; rocuronium IV 1.2 mg/kg was administered. Mask ventilation became progressively more difficult after the administration of rocuronium despite vigorous jaw thrust and placement of an appropriately sized oral airway. Three attempts at rigid laryngoscopy were made—the first two by the initial anesthetist and the third by another senior colleague who was called to assist. Having optimized head and neck position, Macintosh 3, 4 and McCoy blades were used without acquiring a view even of the arytenoids. Between laryngoscopy attempts, manual ventilation was attempted using a two-operator technique; these attempts, however, were unsuccessful. Insertion of a laryngeal mask airway did not enable effective manual ventilation. These attempts at securing a patent airway had taken approximately 4 minutes. The patient became profoundly hypoxic with SpO<sub>2</sub> <80%. While urgent preparation was made for cricothyrotomy, sugammadex 16 mg/kg was administered by rapid IV bolus (the drug was available because trials of sugammadex were underway at the institution). Ninety seconds later, it became possible to deliver

a breath (100% oxygen) to the patient's lungs via face mask and Guedel airway. Shortly afterward, the patient resumed spontaneous ventilation and regained consciousness. SpO<sub>2</sub> rapidly returned to 97% to 99%. Reassessment of the patient revealed a TOF ratio of 0.9, 115 seconds after sugammadex administration (Fig. 53.1).

The patient was fully conscious, alert, well oriented, neurologically intact, hemodynamically stable, and thereafter maintained oxygen saturation of 100% on room air. She was observed for 2 hours in a postanesthetic care unit and was stable without any signs of recurarization. After complete recovery from anesthesia, a full explanation of the events was made to the patient, and the events were recorded in detail in her medical record. The patient was provided with written information regarding her airway management and was asked to relay this to any future anesthetist and to her primary care physician. She was also advised about the option of obtaining a Medic Alert bracelet. Her surgery was rescheduled, and awake fiberoptic intubation was planned.

## CASE DISCUSSION

Sugammadex (Org 25969) is the first selective muscle relaxant binding agent, designed to reverse the steroidal neuromuscular blocking agents (NMBAs), particularly rocuronium.<sup>1</sup> It is a modified  $\gamma$ -cyclodextrin, forms inactive tight 1:1 complexes with, and functions as an irreversible chelating agent for aminosteroidal NMBAs. The administration of sugammadex results in a rapid decrease in the concentration of free rocuronium in the plasma and subsequently in the synaptic cleft at the neuromuscular junction, resulting in rapid normalization of neuromuscular function. Sugammadex has no effect on acetylcholinesterase or any receptor system in the body. Therefore, the need for administering anticholinesterases and anticholinergic (-muscarinic) agents and the associated adverse effects are avoided. Sugammadex-rocuronium complexes are highly hydrophilic and are therefore excreted rapidly and in a dose-dependent manner. Sugammadex is biologically inactive and appears to be safe and well tolerated by patients.<sup>2</sup> Sugammadex reverses profound NMB induced by aminosteroidal nondepolarizing NMB agents rapidly and effectively in a dose-dependent manner.<sup>3-5</sup> The optimal dose required to reverse profound blockade has not yet been fully elucidated. However, sugammadex administration in doses of 4, 8, 12, and 16 mg/kg resulted in reversal of profound rocuronium-induced



**Figure 53.1** • TOF-Watch SX trace (Bluestar Enterprises, Inc, Chanhassen, MN) of the twitch height and T4/T1 ratio after IV administration of rocuronium and sugammadex. Recovery of twitch height (T1) of 90% and TOF ratio of 0.9 returned approximately 115 seconds after sugammadex administration.

NMB to a TOF ratio of 0.9 in (mean values) of 15.8, 2.8, 1.4 and 1.9 minutes, respectively.<sup>3</sup> (The TOF ratio taken to indicate adequate reversal/recovery from NMB is 0.9, as this level is required for normal function of vital muscle groups, including those of the pharynx, to avoid postoperative respiratory complications.<sup>6,7</sup>)

Administering sugammadex in clinical practice could decrease the incidence of postoperative residual curarization. Use of sugammadex could also facilitate the use of rocuronium for rapid sequence induction by providing a faster onset/offset of NMB profile compared with succinylcholine. As in the patient described in this case, sugammadex offers the potential to rapidly terminate profound NMB if the anesthetist is confronted with a “cannot intubate, cannot ventilate” situation.

#### KEY MESSAGES

1. Sugammadex is a selective, novel reversal agent of NMB induced by aminosteroid nondepolarizing NMB agents.
2. Administration of sugammadex 8 mg/kg can reverse profound rocuronium-induced NMB in approximately 90 seconds.
3. A TOF ratio of 0.9 or greater is the threshold that corresponds to adequacy of reversal of/recovery from NMB.

#### QUESTIONS

1. What is the mechanism of action of sugammadex?

Answer: Sugammadex is a modified  $\gamma$ -cyclodextrin, forms inactive tight 1:1 complexes with, and functions as

an irreversible chelating agent for aminosteroidal NMBAs.

2. What is the TOF ratio normally accepted to indicate adequate reversal of /recovery from NMB?

Answer: 0.9

3. What hemodynamic adverse effects are associated with sugammadex administration?

Answer: None of clinical importance. Sugammadex is biologically inactive and appears to be safe and well tolerated by patients.<sup>2</sup>

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# Awareness During Anesthesia

Justin Lane

## **CASE** FORMAT: STEP BY STEP

A 36-year-old primigravida presented for emergency ovarian cystectomy. At 30 weeks' gestation, she had been in the hospital for 2 days with severe abdominal pain, nausea, and vomiting. Intramuscular pethidine (meper-idine) 50 mg and prochlorperazine 12.5 mg were administered to control the symptoms. The patient, a nurse, had no history of anesthesia-related problems.

On assessment the patient, was found to be normotensive (blood pressure, 115/75 mm Hg), with a pulse rate of 92 beats per minute. Her blood glucose was normal, and in her laboratory workup, it was noted that she had an increased white blood cell count  $17 \times 10^9/L$  and serum urea 11 mg/dL. An ultrasound of the patient's abdomen and pelvis confirmed the diagnosis of ovarian cyst torsion. Assessment of her upper airway revealed Mallampati grade II and thyromental distance of 7 cm. Her incisor separation and mandibular mobility were normal. In view of her history and abnormal serum urea, she was commenced on Hartmann's solution at 200 mL per hour to improve her hydration status before surgery. The anesthetic plan was discussed with the patient. A general anesthetic was described, using a "rapid sequence induction" technique, and a transversus abdominis plane block<sup>1</sup> was to be performed intraoperatively for analgesia.

Following application of standard monitors, a rapid sequence induction of anesthesia and tracheal intubation were performed using sodium thiopentone (5 mg/kg) and suxamethonium (1.5 mg/kg) after denitrogenation<sup>2</sup> (preoxygenation with 100% oxygen for 5 minutes). A wedge was placed under the patient's right buttock to decrease the likelihood of supine hypotension. Sevoflurane End tidal (ET) 0.5% to 0.8% in nitrous oxide/oxygen (50:50 mixture), vecuronium, and fentanyl were administered according to the anesthesiologist's clinical judgment. Although BIS monitoring<sup>3</sup> (Aspect Medical Systems, Norwood, MA) was applied (and BIS was <60 throughout the surgery), the anesthesiologist titrated sevoflurane administration according to the patient's heart rate and blood pressure rather than to the BIS value. The difficult airway cart was kept in the operating room. A fetal monitor was applied before induction and was monitored by the attending obstetrician.

## **What factors relevant to this case influence the risk of intraoperative awareness?**

Pregnancy is associated with as great as 30% decrease in minimum alveolar concentration value.<sup>2</sup> Analysis of the American Society of Anesthesiologists closed claims database<sup>4</sup> has identified five factors that increase the risk of recall under general anesthesia: (a) female gender, (b) gynecological/obstetrical procedures, (c) use of opioids, (d) use of muscle relaxants, (e) and lack of use of a volatile anesthetic agent. At least four of these factors apply to the patient in this case. It is likely that the emergency nature of the procedure also increases the risk.

Following an uneventful surgical procedure, the patient's trachea was extubated, and she was transferred to the postanesthesia care unit. Routine postanesthesia monitoring was carried out in the postanesthesia care unit. A combination of regular intravenous paracetamol every 6 hours and intramuscular pethidine (meper-idine) 50 mg every 4 hours was prescribed as were antiemetics and supplemental oxygen. The transverse abdominis plane (TA) block performed intraoperatively appeared to be effective, as no analgesics were administered in the postanesthesia care unit. Hartmann's solution 125 mL per hour was administered until the patient could tolerate fluids orally.

On the second postoperative day, the patient informed the surgeon that she thought she recalled hearing alarms and people discussing her case while the operation was in progress.

## **What is awareness under anesthesia?**

Awareness is a rare complication of general anesthesia, which can have serious psychological sequelae for the patient and serious financial implications for the hospital in which it occurs. It can be classified as: (a) awareness with explicit memory—the patient has conscious recollection of intraoperative events or (b) awareness with implicit memory—the patient has no recollection of intraoperative events.<sup>5</sup>

One to two people per thousand may describe some degree of awareness during their anesthetic; of these, 33% describe pain as part of their experience.<sup>6</sup> More than 50% of "aware" patients describe hearing conversations and sounds within the operating room. About 25% of such patients have experiences relating to endotracheal tube insertion.

Any suggestion of a case of awareness under anesthesia must be followed up (Table 54.1). A review of the anesthetic

**TABLE 54.1** Protocol for Managing Possible Case of Awareness Under Anesthesia<sup>6,10,11</sup>

Visit the patient as soon as possible after the event.
Take a full history and document the patient's exact memory of events, conversations, names, events, and sounds.
Check with other staff who would have been present in theatre during the event.
Review the anaesthesia case notes for evidence of a possible cause, e.g., tachycardia, hypertension in the case of "light anaesthesia."
Give a full explanation of events to the patient.
Plan for patient follow up, including psychological support.
Reassure the patient that further safe general anaesthesia is possible.
Try to determine the cause, review the notes, and check the machine and circuit.
Notify the patient's GP.
Make a detailed record of the event for future reference.

record for the procedure is the first step. The drugs and doses administered should be verified if possible. The levels of volatile agents used alone or in combination with nitrous oxide should be noted. It may be necessary to check the service date on the anesthetic machine, especially the vaporizer. The anesthetist involved in the case should visit the patient, and a witness should be present. The purpose of the visit is to elicit a full history of what the patient experienced and in particular, what he or she heard. It is certainly not to deny the possibility that awareness under anesthesia may have occurred. The patient should be reassured that the claims are taken seriously, and that if she wishes to discuss the issue further, it will be facilitated. Detailed notes regarding the claim should be made at the time of the initial interview. A full range of support services should be made available including psychologists and counselors. If an explanation is possible, it should be provided. The patient will also require reassurance that further anesthesia can be given safely. The patient's general practitioner (primary care doctor) needs to be informed of the incident. The relevant medical indemnity organization and the hospital management should also be informed (Table 54.1).

The responsible anesthetist arranged to meet with the patient in the presence of a hospital representative on the day after she described her experience to the surgeon. The meeting took place in a quiet consulting room, and as she described her recollections, the patient became tearful. She described great difficulty in sleeping and feeling anxious since her operation. She asked what her anesthetist had done that allowed her to be aware of her surroundings during the operation.

**TABLE 54.2** Anesthetic Factors Contributing to Awareness

- |   |
|---|
| • Equipment problems: empty vaporizer, circuit leak               |
| • Drug errors: mislabeled syringes, inadequate drug doses         |
| • Technique: opioid use, light anesthesia in emergency situations |
| • Airway problems: laryngospasm, difficult intubation             |

Reproduced with permission from Osborne G, Bacon A, Runciman K, et al. Crisis management during anaesthesia: awareness and anaesthesia. *Quality and Safety in Health Care* 2005;14:16–25.

### In general, what factors contribute to the occurrence of awareness in modern anesthetic practice?

Patients undergoing specific types of surgical procedures are at greater risk of awareness.<sup>6</sup>

- Cardiac surgery: up to 1 in 100
- Trauma and emergency surgery: up to 1 in 20
- Emergency caesarean section under general anesthesia: 4 in 1000.

The patient's question (regarding the anesthetist's role) is understandable and legitimate, as anesthetic factors can predispose a patient to awareness (Table 54.2).

### KEY MESSAGES

1. Intraoperative awareness occurs more commonly in females and in patients undergoing obstetric-related surgery, cardiac surgery, or emergency procedures.
2. BIS monitoring does not decrease the incidence of intraoperative recall/awareness.<sup>7,8</sup> Intraoperative awareness can occur even when BIS values are within target ranges.<sup>8</sup>
3. Anesthetic departments should have a readily available protocol in place to deal with possible cases of awareness, should they arise.

### QUESTIONS

1. Which patients are at greatest risk of experiencing intraoperative awareness?

Answer: Females and patients undergoing obstetric-related or cardiac surgery or emergency procedures are at greatest risk of experiencing intraoperative awareness.

2. What is the initial appropriate step in responding to a patient's account of awareness?

Answer: The responsible anesthetist should visit the patient as soon as possible after the event.

3. What proportion of patients who describe an awareness experience report pain as a dominant element of their recollection?

Answer: Only 33% of patients who describe an awareness experience report pain as a dominant element of their recollection.

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# Mitochondrial Disease and Anesthesia

Dorothy Breen

## CASE FORMAT: STEP BY STEP

A 16-year-old, 4'7", 50-kg girl with mitochondrial disease was scheduled for a cochlear implant. The anesthesiologist in charge decided to consult his standard textbooks before reviewing the patient. Unfortunately, he found very little information relevant to mitochondrial disease and anaesthesia.

### What is mitochondrial disease, and how does it manifest?

Mitochondrial disease comprises a heterogeneous group of disorders in which the primary abnormalities are errors in the synthesis of mitochondrial proteins caused by defects in nuclear DNA, mitochondrial DNA, or mitochondrial transfer RNA.<sup>1</sup> The mitochondrion is traditionally viewed as the “powerhouse” of the cell, as it contains all the machinery necessary for the Krebs cycle, fatty acid oxidation, and oxidative phosphorylation. The mitochondrion is also unique in that it is the only cellular organelle with its own DNA (mitochondrial DNA). Mitochondrial DNA encodes some of the components of the respiratory chain enzyme complexes. Five enzyme protein complexes are involved in oxidative phosphorylation. Adenosine triphosphate synthesis takes place at complex V. During division of a fertilized ovum, defective mitochondria can become more or less concentrated in one organ or another. Tissues that are postmitotic at birth and have high-energy requirements tend to be most affected (muscle, brain, nerves, retinas, liver, and kidneys), but theoretically, any organ can be involved. Clinical manifestations can range from mild to severe and are progressive over time. All modes of inheritance have been observed, but acquired defects also exist. All these factors contribute to the difficulty in diagnosing patients with mitochondrial disease. These disorders were initially termed the *mitochondrial myopathies*, given that muscle was most often identified as the predominant tissue affected. More recently it is recognized that any organ can be affected at any age; as such, the term *mitochondrial cytopathies* is more appropriate.<sup>2</sup>

Both the girl and her mother were present at the preoperative assessment. The patient's mitochondrial disease had been confirmed as Kearns-Sayre syndrome (KSS). At 9 years of age, she had undergone a muscle biopsy under general anesthesia at a pediatric facility. Her main presenting features were progressive ptosis, skeletal muscle fatigability, and deafness. More recently, she had developed difficulty swallowing and repeated

chest infections. Antibiotics were prescribed 2 days previously for a lower respiratory tract infection. The patient's heart rate was 60 beats per minute, blood pressure was 105/60 mm Hg, and her temperature was 37.9°C. The cardiovascular examination was normal, and her lung fields were clear. There was bilateral ptosis and evidence of skeletal muscle wasting.

### What factors are important in assessing this patient preoperatively?

Preoperative assessment should take account of the potential for multisystem involvement and the varying degrees of severity. Surgery and anesthesia pose a considerable stress to a patient with an already deranged bioenergy metabolism. Infection in this setting places even further demands. Given the presence of pyrexia and the history of a recent respiratory tract infection, it is wise to postpone the surgery. Furthermore, anesthesia in this patient requires much more detailed assessment and planning. KSS, although rare, is one of the better-described entities in the spectrum of mitochondrial cytopathies that exist (Table 55.1). Cardiac involvement is a feature of KSS, and conduction defects are common. Thorough nervous system and neuromuscular assessment should also be performed to determine the extent of skeletal muscle involvement, neurologic deficit, and presence of seizure disorders. Respiratory function is often impaired in patients with mitochondrial disease. It is important to assess the presence of bulbar symptoms, recurrent aspiration, and respiratory muscle weakness.<sup>3,4</sup>

### What tests should be ordered preoperatively?

The results of preoperative spirometry are given in Table 55.2. Full blood count, blood glucose, arterial blood gases, renal, and liver function are presented in Table 55.3. An electrocardiogram, chest radiograph, and echocardiogram were requested and the patient's previous anesthetic record was obtained.

Elevated lactate and blood gas disturbances tend to occur in times of crisis in these disorders. It is important to establish preoperative values, as some patients will have a raised lactate at baseline. The presence of hepatic dysfunction in this patient underscores the multiorgan nature of mitochondrial disease. The finding of left bundle branch block on the electrocardiogram is indicative of the cardiac conduction defects that frequently occur in patients with KSS. Cardiomyopathy has also been described,<sup>5</sup> necessitating an echocardiogram, which was normal in this case. The patient's chest radiograph showed clear lung fields and a normal heart size.

**TABLE 55.1** Some of the Described Clinical Syndromes in Mitochondrial Disease

Acronym/Name	Features
KSS (Kearns-Sayre syndrome)	Ophthalmoplegia, cardiac conduction block, deafness, retinitis pigmentosa, and skeletal muscle weakness
MELAS	Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes
MERRF	Myoclonic epilepsy and ragged red fibers on muscle biopsy
NARP	Neuropathy, ataxia, retinitis pigmentosa, and ptosis
MNGIE	Mitochondrial neurogastrointestinal encephalopathy
LHON	Leber hereditary optic neuropathy. Also Wolff-Parkinson-White syndrome and neuropathy
Leigh's syndrome	Subacute sclerosing encephalopathy

### What type of premedication should be given?

Any form of sedative as a premedication was omitted in this case. Patients with mitochondrial disease are extraordinarily sensitive to sedatives and hypnotics. Respiratory failure and alterations in conscious level can occur even at low doses.

Fasting can precipitate hypoglycemia and a metabolic crisis. The fasting period should be kept as short as possible. If necessary, dextrose infusions can be used to supplement this period. Lactate-containing intravenous fluids should be avoided.

The previous anesthetic record in this instance showed that the patient had previously safely undergone a nontriggering anesthetic. The patient's mother accompanied her to the operating room. Intravenous access was obtained and standard monitoring instituted.

Anesthesia was induced using 10-mg increments of propofol. Once it was established that the patient's airway could be maintained by manual ventilation, 25 mg of atracurium was administered to facilitate tracheal intubation. Analgesia was achieved using paracetamol 1 g and fentanyl 20 µg. Anesthesia was maintained thereafter via propofol infusion and an air/oxygen mixture.

**TABLE 55.2** Spirometry Results

	Predicted	Measured	Predicted (%)
FVC (L)	2.16	1.60	74%
FEV1 (L)	2.14	1.56	73%
FEV1/FVC (%)	99%	98%	99%

Both the FEV1 and FVC are reduced, but the ratio of FEV1/FVC is preserved. These findings are typical of a restrictive lung disease. In this case, it is caused by a respiratory muscle dysfunction. A reduction of FEV1 and FVC in the range 65% to 85% of predicted values signifies that the impairment is mild.

### Was this the most suitable anesthetic technique in this case?

In reality, the safest anesthetic technique for patients with mitochondrial disease is not known. Although many patients have undergone anesthesia safely, there have been case reports describing worsening of underlying neurologic deficit, respiratory failure, high-degree atrioventricular block conduction block, malignant hyperthermia, and death following anesthesia.<sup>6-8</sup>

Because of the limited information available in relation to mitochondrial disease and anesthesia, there are no absolute recommendations. Each anesthetic has to be tailored to the individual patient. Malignant hyperthermia has been reported in the setting of mitochondrial cytopathy.<sup>6,7</sup> There are conflicting opinions, however, as to whether a nontriggering technique is required in mitochondrial disease. The use of inhaled anesthetic agents has been widely described.<sup>9</sup> As with other anesthetic drugs, there appears to be enhanced sensitivity to these agents.<sup>10</sup> In patients with KSS who are at risk of serious arrhythmia, isoflurane and sevoflurane are the preferred agents. On the basis of the patient's previous anesthetic history, inhaled agents were not used in this case. Obtaining previous anesthetic records is vital, as so little is known about safety of anesthesia in patients with these disorders.

Patients with myopathy as a predominant feature of their disease are at risk of suxamethonium-induced hyperkalemia. Notwithstanding the additional risk of malignant hyperthermia, it therefore seems prudent to avoid using this agent.

Propofol has been used safely in many patients with mitochondrial disease despite the fact that it can directly impair mitochondrial function. Caution is required with dosages of all hypnotic agents because of extreme sensitivity. A case of induction of anesthesia after as little as 75 mg of thiopentone in an adult has been described.<sup>11</sup>

Metabolic homeostasis during anesthesia for these patients is an important consideration. Ensuring that the patient does not experience hypothermia and shivering is imperative. A normal glucose and acid-base status should also be maintained.

The presence of left bundle branch block is of concern because patients with KSS undergoing anesthesia are at risk of sudden high-grade atrioventricular block.<sup>12</sup> An isoprenaline infusion and access to external/temporary pacing should be available during anesthesia.

**TABLE 55.3** Full Blood Count, Blood Glucose, Arterial Blood Gases, and Renal and Liver Function

Sodium (135–145 mmol/L)	143	Hemoglobin (11–15 g/dL)	12.5
Potassium (3.5–5.5 mmol/L)	3.7	White blood cells ( $4\text{--}11 \times 10^9/\text{L}$ )	11
Urea (3.0–8.0 mmol/L)	6.2	Red blood cells ( $3.8\text{--}5 \times 10^{12}/\text{L}$ )	4.6
Creatinine (0.07–0.1 mmol/L)	0.07	Platelet count ( $150\text{--}440 \times 10^9/\text{L}$ )	300
Magnesium (0.7–1.0 mmol/L)	0.89	Hematocrit 34%–47%	38
Bilirubin ( $\mu\text{mol}/\text{L}$ )	6	Glucose (4.0–7.5 mmol/L)	6.2
GGT (0–50 U/L)	79	Lactate (0.3–2.0 mEq/L)	1.0
ALP (32–110 U/L)	109	pH (7.35–7.45)	7.38
LDH (110–250 U/L)	298	PaCO <sub>2</sub> (7.35–7.45)	39
AST (0–40 U/L)	256	PaO <sub>2</sub> (85–100 mm Hg)	89
ALT (0–40 U/L)	240	Bicarbonate (22–26 mEq/L)	24

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase. Full blood count, glucose, electrolytes, lactate and renal parameters are all within normal limits. Hepatic dysfunction indicates liver involvement in this case. Reassuringly, there is no evidence of hypercapnic respiratory failure. This finding would be consistent with the spirometry findings of only mild restrictive lung disease.

At the end of the procedure, values obtained for capillary glucose concentration and arterial blood gas estimation were similar to those obtained preoperatively. The patient's temperature was 36.5°C, but there were no twitches evident following train-of-four nerve stimulation. An additional 50 minutes elapsed before four twitches could be elicited. The anesthesiologist then discontinued the propofol and administered 100% oxygen. Following tracheal extubation, the patient was observed in the postanaesthesia care unit for an extended period. Her vital signs were normal, and she appeared comfortable.

### Was the delay in recovery of neuromuscular function to be expected?

Administering a standard dose of atracurium (0.5 mg/kg) in this patient most likely contributed to the prolonged action. As with other anesthetic agents, patients with mitochondrial disease are extraordinarily sensitive. When possible, these agents should be avoided, as they contribute to postoperative respiratory muscle weakness.<sup>13,14</sup> They have been used safely, however, at reduced dosage and with careful monitoring of neuromuscular function. Shorter-acting agents are preferable. The likelihood of renal or hepatic dysfunction (present in this case) makes atracurium and cisatracurium the agents of choice.

### KEY MESSAGES

1. The anesthetic management plan should be tailored to the individual patient.
2. Surgery should be delayed if there is evidence of concurrent infection.
3. Maintenance of normothermia, normoglycemia, and acid-base status is imperative.
4. Lactate-containing solutions should be avoided.

### QUESTIONS

1. Can mitochondrial cytopathies present in adulthood?  
Answer: Yes.
2. Can suxamethonium be safely administered to patients with a mitochondrial cytopathy?  
Answer: No. Opinion is divided on whether such patients are at risk of malignant hyperthermia. Patients with myopathy are at additional risk of suxamethonium induced hyperkalemia.
3. Is Ringer's Lactate a suitable choice as replacement fluid in these patients?  
Answer: No. It contains lactate.

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# Emergence Agitation in Pediatric Patients

Mansoor A. Siddiqui

## CASE FORMAT: REFLECTION

A 5-year-old boy was scheduled for inpatient surgery for elective bilateral myringotomy and ventilator tube insertion. He had been fit and healthy and was not taking any medication. He had not undergone anesthesia in the past. The boy's mother told him that "he is going to the hospital to have his ears fixed, and he is going to be asleep for that." On examination in the day ward, the boy appeared anxious. He was offered toys but, unlike the other children in the ward at that time, he did not play with them. Both of his parents were present, and they also looked anxious. The boy tended to hold onto to his mother and seemed afraid when the nurses or doctors approached.

The patient's heart rate was 120 beats per minute, his blood pressure was 100/50 mm Hg, and his respiratory rate was 25 breaths per minute. He had not taken food or drink for 6 hours before his early morning admission. His upper airway was evaluated as Mallampati grade I with normal dentition (no loose teeth). Informed consent was obtained from his parents for rectal administration of analgesic suppositories. The boy was premedicated with midazolam 0.5 mg/kg orally 30 minutes before his scheduled procedure.

The child's mother accompanied him into the operating room. With standard monitors (electrocardiogram, noninvasive blood pressure, and SpO<sub>2</sub>) in place, anesthesia was induced with oxygen (O<sub>2</sub>)/nitrous oxide (N<sub>2</sub>O) and sevoflurane as he sat in his mother's lap. He was then gently positioned on the operating table. Intravenous (IV) access was obtained with a 22-gauge IV cannula, and a size 2 laryngeal mask airway was inserted. Anesthesia was maintained with sevoflurane (1%–3% inspired) in O<sub>2</sub>/N<sub>2</sub>O (1:2). Diclofenac and paracetamol suppositories were administered before the procedure began.

The procedure was carried out uneventfully in approximately 10 minutes. While the patient was breathing spontaneously, sevoflurane and N<sub>2</sub>O were discontinued (replaced by 100% O<sub>2</sub>), and the laryngeal mask airway was removed while he was still deeply anesthetized. The patient's mouth and oropharynx were gently suctioned. Three minutes later, he started to move his arms and legs and pushed the face mask away. At this stage, he was transferred to the recovery room where he quickly became extremely agitated. He started crying, calling for his "mama." He persistently reached for his ears and vomited once.

During this period of agitation, the patient's heart rate was 140 beats per minute, his blood pressure was 120/70 mm Hg, and his respiratory rate was 35 breaths per minute. He was reassured by the nurse, administered O<sub>2</sub> 40% via face mask, and his mother was invited into the recovery room. His mother's presence helped to calm the child to some extent. Fentanyl 0.5 mcg.kg<sup>-1</sup> was administered intravenously. Over 5 to 10 minutes, his agitated behavior resolved, his heart rate decreased to 95 beats per minute, his blood pressure to 100/50 mm Hg, and his respiratory rate decreased to 25 breaths per minute. The child appeared content and comfortable sitting in his mother's lap.

After the boy was observed and monitored for 30 minutes in the recovery room, he was transferred to the inpatient ward where he remained for another 3 hours until he had eaten, drank, passed urine, and his vitals signs were at preoperative levels. He was reviewed in the inpatient ward by the anesthetist before discharge, whose note in the medical record described him as "comfortable and calm." The patient was discharged home with a prescription for oral analgesics (paracetamol and ibuprofen) "as required" for 5 days.

Two days after discharge, the boy's parents reported to their family doctor that he was reluctant to eat and was sleeping for only 1 to 2 hours at a time. They also noted that, despite receiving the maximum prescribed doses of paracetamol and ibuprofen, he continued to complain of discomfort. They were reassured and advised to continue to administer oral analgesics as required. Three days later, the parents reported that the abnormal eating and sleeping pattern appeared to have resolved.

## CASE DISCUSSION

Emergence agitation can manifest as a number of behavioral patterns that children display during recovery from anesthesia. Two scales that have been used to categorize and grade postoperative behavior in children are the Post Anesthetic Behavior Scale (Table 56.1)<sup>1</sup> and the Pediatric Anesthesia Emergence Delirium scale (Table 56.2).<sup>2</sup>

The Pediatric Anesthesia Emergence Delirium scale score demonstrates negative correlation with a child's age and time to awakening and is significantly greater in children who receive sevoflurane than in those who receive halothane.<sup>2</sup>

**TABLE 56.1** Postanesthetic Behavior Scale

1. Sleeping
2. Awake, calm
3. Irritable, crying
4. Inconsolable crying
5. Severe restlessness, disorientation, thrashing around

Reproduced with permission from Cole JW, Murray DJ, McAkiter JD, et al. Emergence behaviour in children: defining the incidence of excitement and agitation following anesthesia. *Pediatr Anesth* 2002;12:442–447.

Emergence agitation is distressing for the child and his or her parents; its incidence will also influence the numbers of nurses needed to staff the recovery room. It can be associated with physical injury and can prolong the patient's stay in the postanesthetic care unit/recovery room<sup>3</sup> (Table 56.3).

## STRATEGIES TO DECREASE EMERGENCE AGITATION

It is important to identify patients with risk factors for emergence agitation, so that appropriate measures can be taken.

### Anxiety

As many as 65% of children undergoing anesthesia and surgery develop intense anxiety, preoperatively.<sup>4</sup> Preoperative anxiety is a subjective feeling of tension, apprehension, nervousness, and worry. Some of the causes of increased anxiety include separation from parents, uncertainty about anesthesia or surgery and about the outcome of the operation.<sup>5</sup> Preoperative anxiety is an important etiological factor in the development of emergence agitation.

The incidence of postoperative agitation/delirium is greater in anxious (9.7%) compared with nonanxious (1.5%) children.<sup>3</sup> Increased preoperative anxiety is also associated with greater postoperative pain, analgesic consumption, postoperative anxiety, sleep disturbance, and altered eating patterns in 5- to 12-year-old children.<sup>3</sup> Preoperative preparation of children, their parents, and their environment are

**TABLE 56.2** Pediatric Anesthesia Emergence Delirium Scale

1. The child makes eye contact with the caregiver.
2. The child's action is purposeful.
3. The child is aware of his or her surrounding.
4. The child is restless.
5. The child is inconsolable.

Reproduced with permission from Sikich N, Lerman J. Development and psychometric evaluation of the pediatric anesthesia emergence delirium scale. *Anesthesiology* 2004;100:1138–1145.

**TABLE 56.3** Possible Etiological Factors Related to Emergence Agitation

#### Patient Factors

Age<sup>14,15</sup>

Child's temperament<sup>15</sup>

Preoperative anxiety<sup>9</sup>

Parent's anxiety<sup>11</sup>

Hypoxia<sup>36</sup>

Hypercarbia<sup>36</sup>

Hypoglycemia<sup>36</sup>

Hyponatremia<sup>36</sup>

#### Surgical Factors

Otorhinolaryngologic surgery<sup>14,15</sup>

Pain<sup>16,19</sup>

#### Anesthetic Factors

Rapid emergence<sup>19</sup>

Choice of inhalational agent (60% with sevoflurane vs. 20% with halothane)<sup>19</sup>

Intrinsic characteristics of anesthetic agents<sup>16,37,38</sup>

Residual drug effects (e.g., ketamine, droperidol, hyoscine, atropine)<sup>36</sup>

Midazolam<sup>1</sup>

important in decreasing preoperative anxiety. Preparing children for surgery can prevent psychological and behavioral manifestations of anxiety.<sup>6</sup> Various distraction techniques have been used to decrease preoperative anxiety in the anesthetic induction room, the including presence of clown doctors<sup>7</sup> and a handheld video game.<sup>8</sup>

### Temperament

A child's baseline temperament may be associated with the likelihood of his or her developing emergence agitation. Children with a history of temper tantrums are more likely to develop emergence agitation.<sup>9</sup> Various scales exist to assess a child's baseline temperament. One such scale is EASI (emotionality, activity, sociability, and impulsivity), for which reliability has been demonstrated.<sup>10</sup> Younger, more emotional, more impulsive, and less sociable children are more likely to develop emergence agitation. Parents of children in this group were also significantly more anxious.<sup>11</sup>

### Parental Presence During Anesthesia Induction

Parental presence during induction of anesthesia can be used to treat or reduce preanesthetic anxiety. It has been shown to enhance the effect of oral midazolam premedication on emergence behavior of children undergoing general anesthesia.<sup>12</sup> Parental presence has no additive effect on the child's compliance during the anesthetic induction.<sup>12</sup> A combination of

written, pictorial, and verbal information would improve the process of informed consent.<sup>13</sup>

## Age

Emergence agitation is observed more frequently in preschool children.<sup>14,15</sup> Possible etiologic factors include psychological immaturity, genetic predisposition, and the type of procedure.<sup>1,16–18</sup>

## Anesthetic Factors

Emergence agitation occurs in 60% of children after sevoflurane anesthesia.<sup>19</sup> A central nervous system excitatory effect of sevoflurane<sup>20</sup> and epileptiform activity during induction with sevoflurane have been reported.<sup>21</sup> Induction using sevoflurane alone is associated with a greater incidence of emergence agitation compared with when N<sub>2</sub>O is coadministered (35% vs. 5%).<sup>22</sup> Whether awakening occurs rapidly or slowly does not appear to influence the incidence of emergence agitation (35.7% vs. 32, 6% respectively)<sup>16</sup> (Table 56.4).

## Surgical Factors and Adjunct Medications

Surgical procedures involving otorhinolaryngologic surgery and head and neck surgery are associated with a greater incidence of emergence agitation. It has been speculated that this is caused by a “sense of suffocation.”<sup>23</sup>

Postoperative pain has been consistently implicated as an important cause of emergence agitation.<sup>16,19,23,24</sup> In children, emergence agitation and pain behavior may be indistinguishable.<sup>25</sup> The presence of pain as a predisposing factor to postoperative agitation explains the effectiveness of analgesic drugs, either in prophylaxis or treatment of agitation. Opioid administration considerably decreases the incidence of postoperative agitation<sup>26</sup> (Table 56.5).

One or more of these interventions may be selected for managing children at greatest risk for emergence agitation.

## Long-Term Consequences

Emergence agitation in the recovery room is usually self-limiting and resolves without pharmacologic intervention.<sup>1,3</sup> However, long-term sequelae can result. New maladaptive behaviors such as nightmare crying, enuresis, separation

**TABLE 56.4** Modification of Anesthetic Technique to Minimize Likelihood of Emergence Agitation

• Using nerve blocks to minimize postoperative pain
• Parental presence during induction of anesthesia <sup>12</sup>
• Caudal anesthesia for lower abdominal surgery <sup>38</sup>
• Avoiding inhalational agents especially those with low solubility <sup>19</sup>
• Using total IV anesthesia <sup>37</sup>
• IV bolus of propofol at the end of surgery <sup>39</sup>

**TABLE 56.5** Adjunct Medications

• Midazolam 0.2 mg/kg premedication <sup>40–42</sup>
• Clonidine $\mu$ g/kg orally premedication <sup>43</sup>
• Clonidine 1 to 3 mcg/kg intraoperatively (decreases incidence of emergence agitation from 39% to 0%) <sup>44,45</sup>
• Ketamine 6 mg/kg premedication <sup>46</sup>
• Fentanyl 2 $\mu$ g/kg intranasally intraoperatively (decreases incidence of emergence agitation from 23% to 2%) <sup>19</sup> or 2.5 $\mu$ g/kg intravenously <sup>14,26,47</sup>
• Dexmedetomidine 1 $\mu$ g/kg after anesthetic induction <sup>25,41</sup>
• Ketorolac 1 mg/kg intraoperatively <sup>24</sup>

anxiety, and temper tantrums can occur postoperatively in as many as 50% of children.<sup>4</sup> The Post-Hospital Behaviour Questionnaire is designed to evaluate maladaptive behavioral responses in children after surgery. It has shown good test-retest reliability and is a useful standardized tool for assessing postoperative behavior.<sup>27</sup> Using the Post-Hospital Behaviour Questionnaire, it has been shown that children’s preoperative anxiety and emergence status were significant predictors of presence or absence of new maladaptive behavior.<sup>11</sup> The odds ratio for one or more new-onset maladaptive behaviors is 1.43 for children with marked emergence agitation.<sup>11</sup>

## KEY MESSAGES

1. Emergence delirium in children is defined as “a disturbance in a child’s awareness of and attention to his or her environment with disorientation and perceptual alterations including hypersensitivity to stimuli and hyperactive motor behavior in the immediate postoperative period.”<sup>2</sup>
2. It is usually a self-limiting condition, appearing in the immediate postoperative period and resolving spontaneously in 5 to 15 minutes<sup>28,29</sup> but can last longer in 2% to 3% of patients.<sup>1,30</sup>
3. Emergence agitation is defined as “a state of mild restlessness and mental distress that, unlike delirium, is not always accompanied by a significant change in behavior.”<sup>31</sup>
4. Emergence agitation can result from pain, physiological compromise, or anxiety.<sup>32</sup>
5. As many as 10% to 50% of children (compared with 5% of adults) demonstrate alerted behavior during emergence.<sup>33–35</sup> Age, history of temper tantrums, type of surgery, and the anesthetic technique are important predisposing factors.

## QUESTIONS

### 1. What is emergence delirium and emergence agitation?

Answer: Emergence delirium can be defined as “a disturbance in a child’s awareness of and attention to his or her environment with disorientation and perceptual alterations including hypersensitivity to stimuli and hyperactive motor behavior in the immediate postoperative period.” Emergence agitation can be defined as “a state of mild restlessness and mental distress that does not always suggest a significant change in behavior.”

### 2. What are the possible etiological factors contributing to the development of emergence agitation in children?

Answer: In children, preoperative anxiety, age, temperament, parents’ anxiety, type of surgery, type of anesthetic, and adjunct medications all influence the likelihood of emergence agitation occurring. It is more commonly seen in preschool children, with a history of temper tantrums and those with separation anxiety undergoing ear, nose, and throat surgery under inhalation anesthetic (sevoflurane, in particular). Pain is an important etiological factor.

### 3. How can emergence agitation be prevented?

Answer: In children, methods to decrease preoperative anxiety include careful explanation (written, verbal, pictorial) to the child of what to expect, psychological preparation, parental presence during anesthesia induction, use of distraction techniques such as clowns or handheld video games, premedication (e.g., clonidine), and effective perioperative analgesia. Other methods include avoidance of inhalational anesthetic agents, administering an IV bolus of propofol before waking the child, the use of regional anesthetic techniques such as caudal block, and perioperative administration of fentanyl, clonidine, dexmedetomidine, or ketorolac.

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# The Acute Pain Team Role in Management of a Patient With Traumatic Upper Limb Amputation

Owen O'Sullivan

## **CASE** FORMAT: STEP BY STEP

A 46-year-old fisherman was taken to the emergency room of a small regional hospital on a Saturday morning. An accident in the harbor area resulted in a traumatic (avulsion) amputation of his forearm proximal to the wrist, and paramedics had attended to him at the site within minutes. The amputated limb had been packed in ice, and bleeding was controlled with direct pressure. On arrival to the emergency department, 2 hours after the accident, he walked in with the aid of coworkers and was immediately brought to the resuscitation room.

An emergency medicine physician promptly carried out a primary survey. The patient's upper airway was patent; vesicular breath sounds were audible on auscultation bilaterally. His heart rate was 120 beats per minute; blood pressure, 190/100 mm Hg; and Glasgow Coma Scale, 15/15. No other injuries were identified. Intravenous access was established, blood was sampled for routine investigations (full blood picture, urea and electrolytes, serum glucose, lactate and arterial blood gas analysis were all normal), an intravenous (IV) morphine bolus was administered (increments of 2 mg IV totalling 12 mg over 80 minutes), and prophylactic antibiotics were administered as the trauma team evaluated the injury. It was decided that, in view of the patient's general good condition and the relatively short injury/decision interval, that replantation should be considered at the regional plastic surgical referral service based in a hospital approximately an hour away. It was decided to transfer the patient urgently. Before transfer, the anesthetic service was contacted, as the patient was still in extreme pain despite cumulative administration of morphine 18 mg IV and paracetamol 2 g IV over approximately 4 hours.

### **What is the purpose of relieving or managing pain in patients who have suffered traumatic injury?**

Apart from humanitarian indications for treating pain after trauma, inadequate analgesia can exacerbate the stress response, which can result in myocardial ischemia and stroke. Untreated pain is also associated with complications such as impaired cough and ileus. However, evidence proving that pain control improves morbidity and mortality in this setting

is lacking and (for ethical reasons) difficult to acquire. The more general issue of the association between postoperative pain management and patient outcome has recently been critically reviewed.<sup>1,2</sup>

### **What are the pain management options for this patient?**

The American Society of Anesthesiologists guidelines for the management of acute pain in the perioperative period are summarized in Table 57.1.

At the receiving hospital, the plastic surgeon who decided that the amputated limb was not suitable for replantation assessed the patient. An anesthetist (who had received a medical summary by telephone) arrived to assess the patient. The patient was hemodynamically stable but remained distressed and in pain with a verbal rating scale (VRS) score for pain of 10/10. Having considered the risks and potential benefits (delay in surgery, potential for axillary arterial injury, minimizing operative stress response and anesthetic drug and opioid requirements, and lessening risk of postoperative acute and long-term pain), the anesthetist elected to perform a supraclavicular block and to insert a catheter for continuous titratable analgesia. After explaining the procedure to the patient, full asepsis was observed and the block was performed and catheter inserted under ultrasound guidance using a 21-gauge insulated needle. An initial dose of 25 mL of 0.25% levobupivacaine was administered. The patient was reassessed 20 minutes later, just before transfer and was found to be much more comfortable with a VRS score of 2/10. During this 20-minute interval, the anesthetist provided the acute pain team (APT) (through the on-call pain nurse) with a verbal summary of the case.

Prior to induction of general anesthesia (using a rapid sequence induction technique), the patient reported pain in the limb at rest as VRS of 3/10. Six hours had elapsed since the injury. A further 10 mL of 0.25% bupivacaine was injected through the supraclavicular catheter before surgical incision.

The operation, wound exploration, debridement, and a bone-shortening revision of the stump were uneventful. A continuous infusion of 0.1% bupivacaine (initially 8 mL per hour) was commenced via the supraclavicular catheter at the end of the procedure. Regular paracetamol 1 g IV and diclofenac 75 mg IV were prescribed, as was morphine 10 mg intramuscularly for breakthrough pain. Because the anesthetist was concerned about the risk of the patient developing

**TABLE 57.1** Acute Perioperative Pain Management

Institutional policies and procedures for providing perioperative pain management	<ul style="list-style-type: none"> <li>• Education and training for health care providers</li> <li>• Monitoring of patient outcomes</li> <li>• 24-hour availability of anesthetist providing perioperative pain management</li> <li>• Use of a dedicated acute pain service</li> <li>• Standardized, validated instruments to facilitate the regular evaluation and documentation of pain intensity, the effects of pain therapy, and side effects caused by the therapy</li> </ul>
Preoperative evaluation of the patient	<ul style="list-style-type: none"> <li>• Evaluate patient factors</li> <li>• Type of surgery, expected severity of postoperative pain, underlying medical conditions, the risk-benefit ratio for the available techniques, patient's preferences, or previous experience with pain</li> <li>• A directed pain history, a directed physical examination, and a pain control plan</li> </ul>
Preoperative preparation of the patient	<ul style="list-style-type: none"> <li>• Adjust or continue medications that when suddenly stopped may provoke a withdrawal syndrome</li> <li>• Treatment(s) to reduce preexisting pain and anxiety</li> <li>• Premedication(s) before surgery as part of a multimodal analgesic pain management program</li> <li>• Patient and family education</li> <li>• Include misconceptions that overestimate the risk of adverse effects and addiction</li> </ul>
Perioperative techniques for pain management	<ul style="list-style-type: none"> <li>• Use therapeutic options such as epidural, intrathecal opioids, systemic opioid patient-controlled analgesia, and regional techniques after thoughtfully considering the risks and benefits for the individual patient</li> <li>• Used in preference to intramuscular opioids ordered "as needed"</li> <li>• Special caution should be taken when continuous infusion modalities are used, as drug accumulation may contribute to adverse events</li> <li>• Therapy selected should reflect the individual anesthetist's expertise, as well as the capacity for safe application of the modality in each practice setting (including the ability to recognize and treat adverse effects)</li> </ul>
Multimodal techniques for pain management	<ul style="list-style-type: none"> <li>• Unless contraindicated, all patients should receive an around-the-clock regimen of nonsteroidal anti-inflammatory drugs, COX-2 selective inhibitors, or acetaminophen.</li> <li>• Consider regional blockade with local anesthetics.</li> <li>• Dosing regimens should be administered to optimize efficacy while minimizing the risk of adverse events. The choice of medication, dose, route, and duration of therapy should be individualized.</li> </ul>

Adapted from Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology*. 2004;100:1573–1581.

phantom limb pain (PLP), he also prescribed gabapentin 300 mg orally starting on the first postoperative day (300 mg every 12 hours on day 2 and 300 mg every 8 hours on day 3). A written referral was sent to the APT to facilitate follow-up of the patient's pain management.

### Can phantom symptoms be prevented after traumatic amputation?

Pain perceived at the site previously occupied by an amputated limb is common and can be very difficult to treat. A

Dutch study of upper limb amputees showed that the prevalence of PLP was 51% (95% confidence level, 36%–63%); phantom sensation, 76%; and stump pain, 48.6%.<sup>4</sup> Although most of the patients with PLP reported having "moderate" to "very much" pain, only 4 of 99 respondents received medical treatment for phantom pain. In 77% of cases, the indication for surgery was trauma. The use of N-methyl-D-aspartate receptors has been implicated in the development of PLP, and the use of memantine (an N-methyl-D-aspartate receptor antagonist) in a brachial plexus blockade postoperatively in traumatic upper limb amputations has been

shown to decrease the intensity of PLP (but not beyond 6 months).<sup>5</sup>

Some evidence exists that gabapentin, commonly used in several neuropathic pain syndromes, is useful in treating postamputation PLP.<sup>6</sup> However, a study evaluating its effectiveness when administered for 30 days postoperatively failed to show a reduction in incidence or intensity of postamputation pain.<sup>7</sup> Therefore, its use in the case described is not “evidence based.”

Over the following 24 hours, the patient remained relatively comfortable, self-reporting pain as VRS 2 to 4/10. As his first postoperative day was a Sunday, the APT did not review him until his second postoperative day. At this point, the team completed a full pain history (including previous experience of pain and use of pain medications) and examination including the insertion site of the supraclavicular catheter. Gabapentin was discontinued. The APT visited the patient each day, assessing his pain and modifying its management throughout his admission.

### What is the role of the APT in the management of such patients?

A variety of organizations have recommended establishing structures to provide dedicated postoperative pain service.<sup>3,8</sup> Rawal identified important components of an acute pain service (APS) in a recent review article<sup>9</sup>:

- Designated personnel for provision of 24-hour APS
- Regular assessment and documentation of pain scores at rest and at movement
- Maintaining scores below a predetermined threshold
- Appropriate assessment tools for children and those with cognitive impairment
- Development of protocols to achieve goals for postoperative mobilization and rehabilitation
- Education of ward nurses
- Patient education
- Regular audit (including cost-effectiveness)

More than 10 years after the relevant recommendations of the Royal College of Anaesthetists,<sup>8</sup> a survey showed that 83% of hospitals in the United Kingdom had an established APS. However, most were open only Monday through Friday with reduced out-of-hours coverage with only 5% covering 24 hours.<sup>10</sup> The establishment of an APS is associated with lesser postoperative pain ratings and can decrease postoperative nausea and vomiting and postoperative urinary retention.<sup>11</sup> A review of 10 economic evaluations of APS programs failed to demonstrate their cost-effectiveness definitively. This review was limited by the poor quality of the evaluations.<sup>12</sup> The establishment of an APS is presently a prerequisite for accreditation for training by the Royal College of Anaesthetists<sup>13</sup> and the Australian and New Zealand College of Anaesthetists. To function optimally, an APT must operate as part of a multidisciplinary acute rehabilitation program.<sup>14</sup> To justify provision of sufficient resources to fully implement the APT “concept,” further evidence is required regarding the clinical and economic consequences.

### KEY MESSAGES

1. The American Society of Anesthesiologists guidelines for perioperative pain management include the preoperative assessment and preparation of patients and multimodal techniques for pain management.
2. To function optimally, an APT must operate as part of a multidisciplinary acute rehabilitation program.
3. To date, the cost-effectiveness of establishing an APT has not been definitively established.

### QUESTIONS

1. What are the important elements of an acute pain team/service?

Answer: The important elements of an acute pain team/service are (a) designated personnel for provision of 24-hour APS, (b) regular assessment and documentation of pain scores, (c) development of protocols to achieve goals for postoperative mobilization and rehabilitation, (d) education of ward nurses, (e) patient education, and (f) regular audit (including cost-effectiveness).

2. What proportion of upper limb amputees will experience phantom limb symptoms?

Answer: The majority of upper limb amputees will experience phantom limb symptoms (pain, 51%; phantom sensation, 76%).<sup>4</sup>

3. Is establishment of an APT cost-effective?

Answer: Although this has not been demonstrated definitively to date, a body of related evidence indicates that establishment of an APT may be cost-effective.

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# Occupational Exposure to Anesthetic Agents

Jason Van der Velde

## CASE FORMAT: STEP BY STEP

A trainee anesthesiologist lodged a grievance with her hospital attributing the spontaneous abortion of her third pregnancy to exposure to anesthetic gases at work as a causative factor. The hospital's management strenuously denied these allegations citing that its policy of regularly monitoring the operating rooms' air quality showed that her working environment consistently conformed to international occupational health standards. Opinions within the hospital were divided, and considerable tensions mounted over this emotive issue.

### Does occupational exposure to anesthetic gases represent a health risk to health care workers?

Most occupational exposure limits (OELs) in force today are loosely based on meta-analysis<sup>1-3</sup> of nine major studies<sup>4-12</sup> carried out between 1971 and 1985 that examined the associations between (a) occupational exposure to nitrous oxide (N<sub>2</sub>O) and/or some volatile anesthetic agents and (b) a range of adverse health effects, notably spontaneous abortion. Limitations of these investigations include inadequate power, failure to measure personal exposures, and failure to take account of confounding factors such as the variety or absence of scavenging systems used and any additional environmental pollutants. Several subsequent major studies neither ruled out these concerns, nor demonstrated significant association between exposure and adverse health outcomes.<sup>13-19</sup>

The authors of two large epidemiologic studies have concluded that occupational exposure to volatile agents may be related to immunologic, neurologic, renal, or hepatic toxic effects.<sup>20,21</sup> Observational studies have shown associations between exposure to halogenated agents and a deficit in manual dexterity, headache, depression, anxiety, loss of appetite, memory loss, and change in intellectual function.<sup>22-25</sup> Clearly, it would require substantial collaboration to build a conclusive evidence base.

The adverse health effects associated with N<sub>2</sub>O exposure alone are spontaneous abortion (relative risk  $\cong$  1.3 to 1.9) and infertility.<sup>26,27</sup> If the use of N<sub>2</sub>O is to fall out of favor, it is conceivable that exposure to other volatile anesthetics will increase. This has been specifically investigated using both environmental and personal monitoring. Fortunately, the occupational exposure to sevoflurane is not greater when it is

used alone compared with when sevoflurane and N<sub>2</sub>O are administered in combination.<sup>28</sup>

In rodents, long-term exposure to low concentrations of halogenated anesthetic agents impairs curiosity, exploratory behavior, learning and memory function, and increases anxiety.<sup>29</sup> The behavioral changes related to long-term exposure in humans and its associated risk to professional performance have yet to be thoroughly investigated.

A concern raised by pediatric operating room nurses surrounded the interpretation of maximum safe levels of atmospheric sevoflurane. A maximum limit of 2 parts per million (ppm) in the atmosphere was quoted as that set by national health safety legislation. Yet a hospital staff member recalled 18 ppm being monitored during one of the sampling periods. Operating room staff, becoming increasingly concerned for their own safety, were not satisfied by managerial assurances that the manufacturers' recommended safe limit is 20 ppm.

### What is an OEL ?

The National Institute of Occupational Safety and Health (NIOSH) in the United States America clearly states that it is unable to identify a safe OEL for waste anesthetic gases.<sup>30</sup> Current recommendations from NIOSH are that potential risks should be minimized by "reducing exposures to the greatest extent possible." Table 58.1 lists the range of advised OELs as set by various international health authorities. Unless indicated, they are expressed as a time-weighted average exposure in an 8-hour working day.<sup>31</sup>

Manufacturers advise a maximum exposure limit to known hazards. In a recent study, formation of micronucleated lymphocytes was compared in two groups of anesthetic personnel exposed to different levels of waste anesthetic agents. The results indicate that the current range of international limits appears to be appropriate (at least in terms of this marker).<sup>32</sup>

Some staff members believed that volatile anesthetic agents were efficiently scavenged in the pediatric operating rooms, whereas others were convinced that, if they could smell the agents, the concentrations present could not be "safe."

### What is the difference between personal exposure risk and monitored environmental level?

Operating room anesthetic agent concentrations are usually monitored from a fixed point in the room using photoacoustic infrared spectrometry, "monitored environmental level." Because of air movement and scavenging, anesthetic

**TABLE 58.1** Recommended Occupational Exposure Levels for Anesthetic Vapors in Various Countries

	<b>N<sub>2</sub>O</b>	<b>Halothane</b>	<b>Enflurane</b>	<b>Isoflurane</b>	<b>Sevoflurane</b>	<b>Desflurane</b>
Austria	–	5	–	–	–	–
Denmark	100	5	2	–	–	–
France	–	2	–	–	–	–
Germany	100	5	20	–	–	–
Great Britain	100	10	50	50	–	–
Italy	100	–	–	–	–	–
Norway	100	5	2	2	–	–
Sweden	100	5	10	10	–	–
Switzerland	100	5	10	10	–	–
US-NIOSH	25	2	2	2	2	2
US-ACGIH	50	50	75	–	–	–

US-NIOSH, National Institute of Occupational Safety and Health; US-ACGIH, American Conference of Governmental Industrial Hygienists.

agent levels may not be uniform throughout the room. By placing the sampling device at the shoulder of a staff member, that is, sampling directly from their personal breathing zone, a more accurate “personal exposure level” may be measured. Inhalational induction with sevoflurane and N<sub>2</sub>O in pediatric practice was found to violate NIOSH-recommended personal exposure levels approximately 50% of the time based on the personal samples but not in the room samples.<sup>33</sup> This personal exposure risk appears to strongly correlate with anesthetic technique and training.

During maintenance of pediatric anesthesia, the use of uncuffed endotracheal tubes and the Ayres T-Piece can lead to greater monitored environmental levels of anesthetic agents.<sup>34</sup> OELs are, however, rarely violated provided efficient pressure/exhaust ventilation, above 12 air exchanges per hour, and efficient active scavenging systems are in place.

Personal exposure risk monitoring reveals that during maintenance of anesthesia with laryngeal mask airways in adults, sevoflurane concentrations frequently exceed 2 ppm and 50 ppm for N<sub>2</sub>O. Alarmingly, these findings occurred despite the use of low-flow circle circuits, gas scavenging, and correct laryngeal mask airway insertion technique and sizing.<sup>35</sup>

To address increasing staff concerns, the hospital management instituted a thorough review of the areas of the hospital where anesthetic agents were administered or where patients recovering from anesthesia were monitored.

### Do areas other than operating rooms pose a risk of occupational exposure to anesthetic agents?

The monitoring for environmental pollutants by direct reading instrumentation such as photoacoustic infrared spectrometry is expensive and restricts normal staff movements, potentially leading to spurious results.

Personal environmental sampling using passive diffusion tubes or by urine collection is cost-effective and a method that staff find both acceptable and convenient. The use of gas

chromatography-mass spectrometry for determination of N<sub>2</sub>O and sevoflurane in urine and environmental samples is accurate and sufficient for this purpose.

The unscavenged use of on-demand N<sub>2</sub>O:O<sub>2</sub> in poorly ventilated labor rooms is widespread. There is a strong positive correlation between environmental concentrations and midwives’ biological uptake of N<sub>2</sub>O. N<sub>2</sub>O in biological tissues is poorly soluble and therefore should be eliminated rapidly between shifts. Interestingly, 50% of midwives studied had non-zero baseline values of N<sub>2</sub>O in their urine on arrival to the workplace and these 50% showed very high levels.<sup>36</sup>

It is unlikely that staff working in postanesthesia care units are exposed to important amounts of volatile agents from the low concentrations expired by recovering patients. When compared with their colleagues on surgical wards, biological concentrations of N<sub>2</sub>O for recovery room personnel were 3.1 ppm versus 1.17 ppm.<sup>37</sup>

Following this risk assessment, a number of simple strategies were investigated to reduce staff exposure.

### What means are available to minimize occupational exposure of health care workers to anesthetic agents?

**Scavenging** When Mapleson D circuits were equipped with an airway pressure-limiting valve allowing direct connection to an anesthetic gas extractor, the ambient levels of sevoflurane and N<sub>2</sub>O measured in the breathing area around the anesthesiologist decreased from 7 (26) to 1.1 (1) ppm ( $p < 0.001$ ).<sup>38</sup>

**Ventilation** When surgeons and scrub nurses were asked about symptoms related to occupational exposure, a greater incidence of noticing a “smell of gas” was registered for the group without an extractor (87% vs. 11% in the extractor group,  $p = 0.003$ ). Higher rates were also found for general discomfort (62% vs. 11%,  $p = 0.05$ ), nausea (62% vs. 0%,  $p = 0.009$ ), and headache (62% vs. 0%,  $p = 0.009$ ) in the absence of the extractor.

*Anesthetic Practice* The practice of anesthesiology is not confined to the operating room. Investigations examining the effects of sevoflurane and N<sub>2</sub>O exposure on gene mutation,<sup>39</sup> specifically, the incidence of sister chromatid exchanges in peripheral lymphocytes, concluded that a 2-month rotation out of the operating room environment returned the incidence of gene mutation to that of the general population.

### KEY MESSAGES

1. Definitive (level 1) evidence regarding the risk of occupational exposure to anesthetic agents is lacking.
2. Personal environmental monitoring provides the best measure of occupational exposure to anesthetic agents.
3. Exposure can be decreased through training, technical innovation, and optimizing working practices.

### QUESTIONS

1. Which adverse health outcomes may be associated with occupational exposure to N<sub>2</sub>O?

Answer: The adverse health effects associated with N<sub>2</sub>O exposure alone include spontaneous abortion (relative risk  $\cong$  1.3 to 1.9) and infertility.

2. What means are available to minimize occupational exposure of health care workers to anesthetic agents?

Answer: Optimizing scavenging, environmental ventilation, anesthetic practice, and regular personal monitoring can minimize occupational exposure of health care workers to anesthetic agents.

3. What is NIOSH?

Answer: NIOSH stands for the National Institute of Occupational Safety and Health (in the United States).

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# Fetal Oxygen Saturation and Caesarean Section

Siun Burke

## **CASE** FORMAT: STEP BY STEP

A 28-year-old, 100-kg, term primigravida presented in labor requesting epidural analgesia.

### **What are the risks associated with epidural analgesia in labor?**

See Table 59.1.

The epidural was inserted on the second attempt, and a bolus dose of 10 mL 0.25% bupivacaine with 50 µg of fentanyl was administered followed by an epidural infusion of levobupivacaine 0.125% at 12 mL per hour. The patient, however, continued to complain of discomfort with each contraction. Four hours later, a vaginal examination revealed minimal progress, and the patient was scheduled for an emergency lower-segment caesarean section.

### **How should the anesthetist proceed?**

A detailed preoperative assessment will enable early identification of a poorly functioning epidural and any potential problems if spinal or general anesthesia is deemed necessary.

On preoperative assessment, the patient's past medical history was unremarkable. However, she had a short stature and was morbidly obese with a body mass index of 46 kg/m<sup>2</sup>. Examination revealed a Mallampati grade III airway.

The patient's vital signs were normal; her blood pressure was 120/64 mm Hg, and her heart rate was 92 beats per minute. The epidural block was assessed, and despite augmentation with 20 mL of bupivacaine 0.5%, only extended to T10 and was patchy. The anesthetist explained to the patient that the epidural was ineffective and that the operation would proceed under spinal anesthesia. The patient asked whether any form of anesthesia was superior in terms of neonatal outcome.

### **How should the anesthetist respond to this query?**

A meta-analysis comparing different methods of anesthesia for caesarean section and neonatal acid base status analyzed 27 studies and concluded that spinal anesthesia could not be considered safer than general anesthesia or epidural anesthesia for the fetus.<sup>1</sup>

Adverse maternal circulatory changes associated with spinal anesthesia may result from excessive sympathetic blockade, aor-

toic compression, use of vasopressors, and fluid loading.<sup>1</sup> A recent Cochrane review concluded that there was no evidence to show that regional anesthesia was superior to general anesthesia in terms of major maternal or neonatal outcomes.<sup>2</sup> It must be remembered that the absolute risk of maternal mortality associated with general anesthesia for caesarean section is 32 per million, which is 17-fold greater than that with regional anesthesia.<sup>3</sup> The incidence of failed tracheal intubation in the obstetric population, 1 in 250,<sup>4</sup> is as many as 10 times greater than that in the general population. Recognizing the risks to the mother associated with general anesthesia has led to an increased use of regional anesthesia for caesarean deliveries.

The anesthetist reassured the patient that there was no major difference in neonatal outcome between general, spinal, or epidural anesthesia. In view of her elevated body mass index and potentially difficult airway, he felt regional anesthesia was preferable to general anesthesia.

The patient was prescribed antacid prophylaxis, and a 16-gauge intravenous cannula was inserted. In the operating room, with routine monitors in place, the anesthetist proceeded with spinal anesthesia. Following dural puncture with a 25-gauge pencil-point spinal needle and aspiration of clear cerebrospinal fluid, the anesthetist administered 12.5 mg of hyperbaric bupivacaine intrathecally.

### **What are the risks of administering spinal anesthesia following inadequate epidural for lower-segment caesarean section?**

Spinal anesthesia after epidural analgesia may result in an unpredictable final block height. One retrospective review estimated the incidence of high spinal anesthesia to be 11% in patients after prior failed epidural blockade versus fewer than 1% in patients undergoing spinal anesthesia alone.<sup>5</sup> This may be explained by the volume of the dural sac being restricted by fluid in the epidural space. There is controversy regarding the optimal dose of hyperbaric bupivacaine in this setting; some investigators advocate reducing the dose by 20% to 30%,<sup>6</sup> whereas others believe this increases the risk of a second unsatisfactory block.<sup>7</sup>

Whichever approach is used, early recognition of an inadequate epidural block is important to avoid persisting with further doses of epidural local anesthetic. An assessment of the urgency of the situation will help guide further anesthetic management.

Spinal anesthesia should be followed by careful positioning and frequent block assessment. The parturient should be

**TABLE 59.1** Complications of Epidural Analgesia

<b>Immediate</b>
Hypotension (systolic blood pressure <100 mm Hg or a decrease of 25% below preblock average)
Urinary retention
Local anesthetic-induced convulsions*
Local anesthetic-induced cardiac arrest*
<b>Delayed</b>
Postdural puncture headache
Transient backache
Epidural abscess or meningitis*
Permanent neurologic deficit*
*Very rare. Reproduced with permission from Vincent RD Jr, Chestnut DH. Epidural analgesia during labor. American Family Physician 1998;58: 1785-1792.

assessed regularly for difficulty in phonation, swallowing, breathing, and weakened handgrip. Extra vigilance is required if a bolus has been administered via the epidural in the 30 minutes prior to spinal anesthesia, if the patient weighs more than 120 kg, or if the height is less than 4'8".<sup>6</sup> The use of a combined spinal epidural technique allows a smaller intrathecal dose to be used with the option of "topping up" using the epidural catheter if the block is inadequate.

In this case, the patient was 100 kg, of short stature, and had just received an epidural top-up before spinal anesthesia. After the spinal, the patient's blood pressure decreased to 74/53 mm Hg, and her heart rate dropped to 62 beats per minute. She experienced nausea, removed the wedge, and lay supine. For the first time, late decelerations (fetal heart rate <90 beats per minute) were evident on the cardiograph (Fig. 59.1).

**TABLE 59.2** Determinants of Fetal Oxygenation

Maternal oxygen delivery to the placenta	<ul style="list-style-type: none"> <li>• Uterine artery blood flow</li> <li>• Oxygen capacity of maternal blood</li> <li>• Oxygen affinity of maternal blood</li> </ul>
Oxygen transfer across the placenta	<ul style="list-style-type: none"> <li>• Oxygen-diffusing capacity</li> </ul>
Fetal oxygen-carrying capacity	<ul style="list-style-type: none"> <li>• Umbilical vein blood flow</li> <li>• Oxygen capacity of fetal blood</li> <li>• Oxygen affinity of fetal blood</li> </ul>

**What are the determinants of fetal oxygenation?**

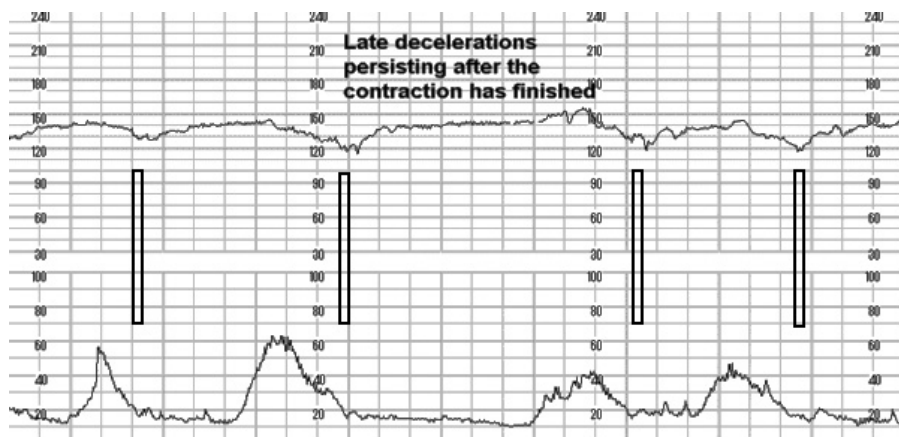
Oxygen delivery to the fetus (mmol/min) is given by the product of umbilical blood flow and the oxygen content of umbilical venous blood (Table 59.2).

Maternal oxygen delivery to the placenta is affected by uterine artery blood flow, oxygen content of maternal uterine artery blood, hemoglobin concentration, and saturation. Uterine blood flow at term is 10% of cardiac output. Hypotension, uterine contractions, and vasoconstriction can all decrease uterine blood flow.

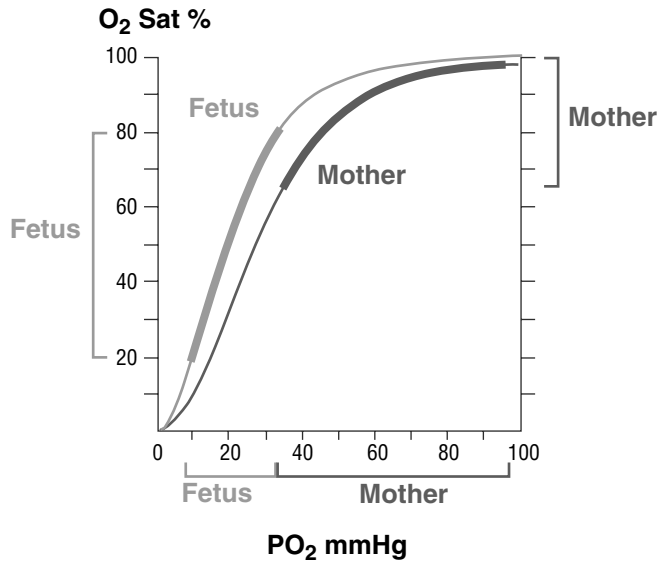
In the case described, maternal hypotension and desaturation reduced oxygen delivery to the placenta.

The fetus has about 42 mL of oxygen reserves, and its oxygen consumption is 20 mL/min. A fetus deprived of oxygen can survive 10 minutes (rather than 2 minutes one might expect from these values) by shunting blood flow to vital organs and decreasing oxygen consumption.

The fetus has many protective mechanisms to ensure its oxygen extraction capacity. The hemoglobin concentration is higher (15 to 16 g/dL). Fetal hemoglobin is 80% to 90% saturated at a pO<sub>2</sub> of 35mm Hg, whereas adult hemoglobin is only



**Figure 59.1 • Cardiograph Showing Late Decelerations.**



**Figure 59.2 • Fetal and Adult Oxyhemoglobin Dissociation Curves.**

30% saturated at this  $pO_2$ . This difference is caused by a leftward shift in the fetal oxyhemoglobin dissociation curve.<sup>8</sup> (Fig. 59.2).

Supplemental oxygen (6 L per minute via 40% Ventimask [Flexicare Medical Limited, Mid Glamorgan, United Kingdom]), Hartmann's solution 500 mL, and repeated doses of phenylephrine (100  $\mu$ g,  $\times 3$ ) were administered rapidly, and the patient was repositioned with a left lateral tilt. Her blood pressure improved to 90/53 mm Hg, and  $SpO_2$  increased to 95%.

### Is supplemental oxygen beneficial during a caesarean section?

Studies during general anesthesia for caesarean delivery have shown improved  $pO_2$  and Apgar scores with increased inhaled fractions of oxygen. A study of hyperoxia versus normoxia in epidural anesthesia showed better umbilical artery base excess in the hyperoxia group.<sup>9</sup> Some investigators believe maternal hyperoxia is necessary to build up a reserve of fetal  $pO_2$ , as fetal oxygenation ceases after uterine incision after which unexpected delays could cause damage.<sup>10</sup> Patients who undergo spinal anesthesia may be under particular risk because of its restrictive effect on ventilation.

It has been argued that maternal hyperoxia could cause hypoventilation,  $CO_2$  retention, and subsequent placental vasoconstriction. Administration of oxygen to the mother at 5 liters per minute has been shown to reduce intervillous blood flow significantly.<sup>11</sup> A maternal  $FiO_2$  of 0.6 produces a significant increase in free radical activity in both maternal and fetal blood.<sup>12</sup> Nevertheless, maternal hyperoxia during labor has been shown to increase  $pO_2$  in the compromised fetus.<sup>1</sup>

Five minutes later, the patient became distressed, she started to complain of paraesthesia in her arms and difficulty breathing, and then her voice became weak. On examination, there was only minimal chest rise with each inspiration. The oxygen saturation fell to 82%.

**TABLE 59.3 Umbilical Artery Blood Gas**

		Normal Values
$pO_2$	1.8 kPa	2.38 $\pm$ 0.9
$pCO_2$	7.2 kPa	7.49 $\pm$ 1.13
pH	6.98	7.24 $\pm$ 0.07
Base excess	-14	-3.6 $\pm$ 2.7
Lactate	6.4	<2

### How should the anesthetist proceed?

Management of High/Total spinal anesthesia requires early detection and supportive management of airway, breathing, and circulation.

Following preoxygenation, application of cricoid pressure, and induction of general anesthesia, laryngoscopy revealed a Cormack and Lehane grade 3 view.

It was not possible to intubate the trachea, and the oxygen saturation decreased below 70%. The anesthetist managed to manually ventilate the patient via a face mask, and the oxygen saturation increased to 82%.

After several minutes, a baby boy was born. His Apgar scores were 2 and 3 at 1 and 5 minutes, respectively (Table 59.3).

### Is umbilical cord blood gas analysis useful in the assessment of the newborn?

Umbilical cord blood gas analysis is now recommended in all high-risk deliveries by both the British and American Colleges of Obstetrics and Gynecology. Umbilical artery pH has a metabolic and a respiratory component, the latter largely determined by maternal respiration. Isolated fetal respiratory acidosis is usually the result of short-lived impairment in the uteroplacental or fetoplacental circulation, and ongoing impairment results in progressive metabolic acidosis caused by anaerobic glycolysis. Consequently, most severe fetal acidosis is mixed. Base excess is independent of respiration and is thus a better index of the metabolic component and key to evaluating the recent prenatal environment.<sup>1</sup> Base excess usually decreases by a total of 3 mmol/L in uncomplicated labor and by 1 mmol/L every 30 minutes under conditions when there are frequent heart rate decelerations. The most profound fetal compromise, uterine rupture, changes pH by 1 mmol/L every 2 to 3 minutes.<sup>13</sup>

Portman et al. developed a validated score for predicting multiorgan impairment following perinatal asphyxia. They found that a score combining a measure of cardiograph abnormality, umbilical artery base excess, and low 5-minute Apgar score was strongly associated with morbidity.<sup>14</sup> Lactate measured in umbilical cord blood is almost entirely fetal in origin. Umbilical cord lactate has been shown to correlate with fetal pH and base excess.<sup>15</sup>

The neonate was intubated, stabilized, and transferred to the neonatal intensive care unit. A senior anesthetist arrived, and the mother was intubated with the aid of a gum elastic bougie. The case proceeded uneventfully, and the mother was extubated once fully awake in the recovery room. The neonatologist informed her that the baby had two seizures in the preceding hour and his prognosis was guarded.

**KEY MESSAGES**

1. Careful preoperative assessment of the parturient will allow early identification of a poorly functioning epidural and of potential problems with spinal or epidural anesthesia. This review will ensure that senior experienced personnel and all necessary equipment are available in case of emergency.
2. Spinal anesthesia following inadequate epidural blockade can result in an unpredictable final block height. Extra vigilance is required if a bolus has been administered via the epidural in the 30 minutes before spinal anesthesia, if the patient weighs greater than 120 kg or if the height is less than 4'8".
3. Early recognition is a key to management of high total spinal anesthesia. Treatment is supportive and begins by addressing airway, breathing, and circulation.

**QUESTIONS**

1. What population of cardiac output does uterine blood flow constitute at full term?

Answer: 10%

2. Outline the steps that may resolve peripartum fetal acidosis during caesarean delivery.

Answer: Oxygen delivery to the fetus (mmol/min) is given by the product of umbilical blood flow and the oxygen content of umbilical venous blood. Maternal oxygen delivery to the placenta is affected by uterine artery blood flow, oxygen content of maternal uterine artery blood, hemoglobin concentration, and saturation. Treating maternal hypotension with a fluid bolus or vasoconstrictors will help to improve fetal oxygenation. A left lateral tilt will reduce the incidence of aortocaval compression, which may compromise fetal blood flow. The oxygen content of maternal blood can be increased by supplying the parturient with supplemental oxygen.

3. What is the clinical presentation of total spinal anesthesia?

Answer: Total spinal anesthesia may present with increased maternal anxiety, hypotension, bradycardia,

paraesthesia and weakness of the arms and hands, difficulty breathing, altered phonation, and loss of consciousness.

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# Vasoconstrictors for Hypotension During Caesarean Section

James O'Driscoll

## **CASE** FORMAT: STEP BY STEP

A fit, healthy 29-year-old primigravida presented for elective lower-segment caesarean section. The indication for surgery was breech presentation of the fetus at 39 weeks' gestation. Preoperative assessment revealed only a history of postoperative nausea and vomiting after a tonsillectomy when the patient was 15 years of age. Hemoglobin concentration was 12.3 g/dL. The options for anesthesia were discussed with the patient, and it was agreed that regional anesthesia in the form of a spinal anesthetic was the most appropriate.

On arrival in the operating room, appropriate monitoring was established (Table 60.1).

### **What does appropriate monitoring mean in this setting?**

At this stage, the appropriate monitors are electrocardiogram, noninvasive blood pressure, and SpO<sub>2</sub>.

A 16-gauge intravenous cannula was inserted after skin infiltration with 1% lidocaine, and 1500 mL of compound sodium lactate was administered intravenously over 20 minutes.

### **What is the rationale for fluid preloading before spinal anesthesia?**

Fluid preloading before spinal anesthesia is done in an attempt to prevent or decrease the degree of hypotension caused by the regional sympathetic blockade. For patients undergoing lower-segment caesarean section, preloading is no more effective than administering fluid at the time or immediately after performance of the block.<sup>1</sup> Colloid fluids have been shown to be more effective than crystalloids for this purpose.<sup>2</sup>

Bupivacaine (0.5% 2 mL) and fentanyl (25 µg) were injected into the intrathecal space with the patient in the sitting position under aseptic conditions using a 25-gauge pencil-point (Whitacre) spinal needle (BD Medical - Medical Surgical Systems, Franklin Lakes, NJ).

### **Does the dose of local anesthetic administered influence the likelihood and degree of hypotension?**

Lesser doses of local anesthetic, particularly with the addition of opioids, appear to decrease the frequency and degree of

hypotension. The most promising preventive strategies are preloading, administering intrathecal opioids (for a local anesthetic-sparing effect), leg compression, or a combination of these methods.<sup>3</sup>

After the spinal anesthetic was administered, the patient was returned to the supine position with left lateral tilt, and ephedrine 6 mg was administered intravenously.

### **Is prophylactic ephedrine effective in preventing hypotension after spinal block?**

Ephedrine has been found to be ineffective in preventing hypotension when used in small doses, and when used in greater doses, it is more likely to cause hypertension.<sup>4</sup>

After 5 minutes, assessment of the patient's perception of cold (ice) revealed a bilateral sensory block to T6 and surgery proceeded. Shortly afterward, the patient complained of nausea, and an additional dose of ephedrine was administered. Her blood pressure remained low at 80/50 mm Hg and did not respond to two additional doses of ephedrine (each 6 mg). At this point, phenylephrine 100 µg was administered intravenously. The patient's systolic blood pressure increased to 110 mm Hg, and her nausea eased. Five minutes later, the patient's blood pressure decreased again (Table 60.1), and she complained of both nausea and discomfort. Again, her blood pressure increased after a bolus of phenylephrine 100 mcg intravenously. Extra doses of phenylephrine were required to maintain her blood pressure at this level, and a live male infant was delivered 25 minutes after the spinal block was administered. His Apgar scores were 9 (at 1 minute) and 10 (at 5 minutes). Umbilical cord pH measurements were arterial, pH 7.2 and venous, pH 7.26. Blood loss during the surgery was approximately 850 mL.

### **Is phenylephrine more effective than ephedrine in treating systemic hypotension in this setting?**

A recent study has shown that phenylephrine is superior to ephedrine when administered by infusion for treatment of hypotension in patients undergoing lower-segment caesarean section under spinal anesthesia. Phenylephrine had less effect on fetal acid-base status, although this finding has not been linked to fetal outcomes in any significant manner.<sup>1,5,6</sup> Although ephedrine and phenylephrine have been the most commonly used and studied agents, other vasoconstrictors such as metaraminol also may be effective.

**TABLE 60.1** Vital Signs

	Initial	Block	5 min	10 min	15 min	20 min	25 min	30 min	35 min
Heart Rate	98	110	92	88	76	120	100	98	102
Non-invasive blood pressure (mm Hg)	130/80	138/72	70/42	80/60	110/80	100/72	98/62	116/68	110/62
SpO <sub>2</sub> (%)	98	95	96	96	97	94	95	96	96

**KEY MESSAGES**

1. Early recognition and treatment of hypotension following spinal block for caesarean section is vital for maintaining maternal comfort. Evidence for adverse fetal outcome is lacking.
2. Several strategies for preventing hypotension have been found to be ineffective when used alone but have shown promise in combination.<sup>3</sup>
3. Ephedrine and phenylephrine are the most commonly used vasoconstrictors in this setting; the latter is more effective for treating systemic hypotension and has potentially fewer effects on the fetus.

for fluid loading but do have the potential to cause adverse effects such as pruritus, allergy, and renal dysfunction.

**3. What is the treatment of choice for systemic hypotension following spinal anesthesia for caesarean section?**

Answer: For treatment of hypotension, phenylephrine is more effective than ephedrine, particularly when used by infusion. Phenylephrine also seems to be beneficial in terms of fetal acid base balance with less effect on cord pH measured at delivery, although this does not seem to be related to fetal outcome unless it is abnormal for another reason. Phenylephrine administered by infusion also seems to be superior to phenylephrine administered by bolus dose alone. The optimal strategy seems to be a combination of techniques with anticipation of hypotension, and rapid treatment is a priority.

**QUESTIONS**

**1. Is prophylactic administration of a vasoconstrictor(s) effective in preventing hypotension during a caesarean section?**

Answer: Administering a vasoconstrictor(s) prophylactically can decrease the frequency and magnitude of hypotension after spinal anesthesia for caesarean section but does not reliably do so. No one agent has been shown to be superior to another in terms of prophylaxis.

**2. Does fluid preloading decrease the incidence or severity of hypotension during caesarean section under spinal anesthesia?**

Answer: Fluid loading is inconsistent in preventing hypotension in this setting. Preloading seems to be no more effective than what is often called: co- (at the time of block) or post- (immediately after block) loading. Colloids have been shown to be superior to crystalloids

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