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Critical Care of Surgical Patients, Part I

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The literature review is compiled with the assistance of an 18-member, international board of editors who are experts in the various focus areas that comprise the specialty of surgery. In addition, the editorial board has representation and expertise in such important fields as medical evidence evaluation, surgical education, outcomes research, standard setting, and performance improvement. *SRGS* is a unique resource because the overview and selected full-text articles provide the reader with the most valuable and pertinent content illuminated with informed opinion and critique. Unnecessary material is eliminated. *SRGS* does not present itself as infallible and the editor-in-chief takes responsibility for the content that appears in each issue. The editor-in-chief and the editorial board recognize that there is no such thing as the "average" surgical patient, and that the information in the literature must be interpreted in the light of the clinical presentation of each individual patient.

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Editor in Chief: Lewis Flint, MD, FACS
Associate Editor: Nicholas Namias, MD, FACS

Introduction | CRITICAL CARE OF SURGICAL PATIENTS, PART I

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Welcome to *Selected Readings in General Surgery (SRGS)*: Critical Care of Surgical Patients, Part I. This issue is the first of a two-part series that will review articles relevant to surgical critical care.

This first issue in our critical care series will review the diagnosis and management of cardiac disorders, pulmonary complications, and acute kidney injuries. Cardiac and respiratory complications are the two most frequent adverse events that occur following injury and general surgical operations. Using modern understandings of cardiac and pulmonary pathophysiology, surgeons can now prevent or manage these events with frequent patient salvage and full recovery. Understanding the pathophysiology and risk factors for critical illness-related kidney injuries can provide useful knowledge that will help surgeons prevent renal injuries, recognize signs of acute kidney dysfunction before permanent renal damage occurs, and implement approaches that will support and maintain renal function in these patients.

In 2016, we lost a great friend and a true pioneer in surgical critical care, Dr. Joseph Civetta. Joe Civetta spent 25 years at the University of Miami innovating approaches to the critically ill surgical patient. He was a leader in the development of cost-effective care protocols and introduced concepts of palliative care into the surgical intensive care unit (ICU). It is an honor to dedicate this series to his memory.

I am indebted to Dr. Nicholas Namias, who was mentored by Dr. Civetta, for providing editorial assistance for this critical care series.

Perioperative Cardiovascular Complications

Evidence of atherosclerotic cardiovascular disease is found at autopsy on nearly all patients dying after the age of 40. Symptoms of atherosclerotic cardiovascular disease become increasingly common as patients age; disease progression occurs in a significant proportion of older patients and cardiovascular disease is the leading cause of death among adults older than 65 years in North America. Increasingly, older patients with moderate-to-severe comorbid cardiovascular diseases are presenting for surgical care. Current data estimate that 60%–80% of postoperative deaths following elective procedures are traceable to cardiovascular complications. In this first section, we will review pertinent data on perioperative cardiac complications. Current information on issues relevant to risk recognition, risk modification, and cardiac event prevention will be covered as well as data pertinent to the diagnosis and management of perioperative myocardial infarction (MI), cardiac failure, and arrhythmias.

Quantifying Risk for Perioperative Cardiac Complications

The effective prevention of perioperative cardiac complications is only possible if patients who are at risk can be identified. Preventive measures will obviously be most effective for patients who are scheduled to undergo elective operations. In this patient group, there will be time for a detailed history and physical examination, laboratory studies, and specific cardiac testing, if indicated. The articles reviewed in this section will detail the fundamental features of perioperative cardiac risk assessment and risk modification.

Recommendations for predicting postoperative cardiovascular complications were provided in the 2014 clinical practice guidelines for prevention and management of cardiovascular complications in patients undergoing noncardiac procedures.[1] The guidelines were sponsored by the American Heart Association/American College of Cardiology and were published in the *Journal of the American College of Cardiology,* 2014. The guidelines define an emergency procedure as an operation for life- and/or limb-threatening conditions where there is no opportunity for preoperative evaluation and optimization of risk. An urgent procedure is one where there is potential for significant threat to life or limb, but a delay of up to 24 hours is possible. A time-sensitive procedure is defined as an operation that can be delayed for one to six weeks for patient evaluation and risk reduction; the final category is an elective procedure that can be delayed up to one year for management of associated cardiovascular conditions. The guidelines document presents a summary of risk factors for perioperative cardiovascular events. Data cited in the document confirm that a recent cardiac event (unstable angina, MI, congestive heart failure) increases risk for postoperative cardiac complications and mortality. Available evidence supports a recommendation for delaying an operation for at least 60 days following a cardiovascular event. Additional data presented in the guidelines suggest that revascularization following a MI (percutaneous or coronary artery bypass) reduces the risk for subsequent postoperative MI. Additional risk factors include older age, diabetes, hypertension, history of stroke, and frailty.

Data confirming increased risk of postoperative MI and cardiac arrest in patients with a preoperative history of MI who have significant angina symptoms were presented in an article by Pandey and coauthors[2] in the *American Journal of Cardiology,* 2015. The authors reviewed data from the American College of Surgeons National Surgical Quality Improvement Program® (ACS NSQIP®) database. They found that significant preoperative angina symptoms in patients with a history of past MI increased the risk of postoperative MI or cardiac arrest by nearly 40% (8.4% vs. 5.5%). The authors concluded that elective and time-sensitive procedures in this patient group be delayed for complete evaluation and optimization of cardiovascular risk factors.

The guidelines[1] recommend that patients suspected of having valvular heart disease undergo preoperative echocardiography for documentation of presence of valvular heart disease and quantification of severity. If the valvular heart disease is severe enough to warrant valve repair or replacement, this should occur prior to any elective noncardiac procedure. Patients with asymptomatic valvular heart disease can undergo a needed noncardiac procedure with

intraoperative monitoring. The guidelines recommend effective communication among cardiologists, surgeons, and anesthesiologists for managing patients with valvular heart disease and implantable electronic cardiac devices.

It is possible to predict postoperative cardiac complications using available risk scoring systems. The guidelines recommend using the revised cardiac risk score (RCRI) or the ACS NSQIP risk calculator. The guidelines acknowledged a limitation of the NSQIP risk calculator: elevated ST segment MI, large troponin elevation, and "chaotic rhythm" were the index events used as risk factors in the creation of the calculator. Also, the risk calculator uses the American Society of Anesthesiology (ASA) risk index, which has shown relatively poor inter-rater reliability. Available evidence does not support the use of biomarkers such as C-reactive protein to improve risk calculations. The guidelines provide recommendations for preoperative cardiac testing (EKG, echocardiography, coronary artery evaluation) based on risk assessment. A table comparing the features of the RCRI and NSQIP risk calculation scores with the 1977 Goldman risk score is provided in an article by Smilowitz and Berger[3] in *Circulation,* 2016 (Figure 1). The article is a concise review of the measures that may be necessary to evaluate and manage cardiac risk when a noncardiac operation is planned; this article is supplied as a full-text reprint accompanying some formats of *SRGS*.

Additional perspective on the revised cardiac risk score was presented in an article by Ford and coauthors[4] in *Annals of Internal Medicine,* 2010. The authors observed that accurate risk scoring is necessary to determine the need for detailed preoperative cardiac testing and to guide the use of preoperative interventions such as β-blocking drugs. A dependable risk scoring system would be useful

Figure 1 Comparison of cardiac risk scores for patients undergoing noncardiac operative procedures. Reproduced from Smilowitz and Berger[3] with permission.

Comparison of Perioperative Risk Calculators

	Goldman Index of Cardiac Risk (1977)	Revised Cardiac Risk Index (1999)	NSQIP Perioperative MI and Cardiac Arrest (MICA) Risk Calculator (2011)	NSQIP Universal Surgical Risk Calculator (2013)
Criteria	• Jugular venous distention or a third heart sound on auscultation • Recent MI within 6 mo • ≥5 PVCs per min • Nonsinus cardiac rhythm or PACs on preoperative ECG • Age >70 • Aortic stenosis • Intraperitoneal, intrathoracic, or aortic surgery • Any emergency surgery	• Cerebrovascular disease • Ischemic heart disease • History of congestive heart failure • Insulin therapy for diabetes mellitus • Serum creatinine ≥2.0 mg/dL • Planned high-risk procedure (intraperitoneal, intrathoracic, or vascular surgery)	• Age • ASA class • Creatinine • Preoperative function • Procedure type (anorectal surgery, aortic, bariatric, brain, breast, cardiac, ENT, foregut/hepato-pancreatobiliary, gallbladder/appendix/ adrenal/spleen, intestinal, neck, obstetric/gynecologic, orthopedic, other abdomen, peripheral vascular, skin, spine, thoracic, urology, vein)	• Age group, y • Sex • Functional status • Emergency case • ASA class • Steroid use for chronic condition • Ascites within 30 d preoperatively • System sepsis within 48 h preoperatively • Ventilator dependent • Disseminated cancer • Diabetes mellitus • Hypertension requiring medication • Previous cardiac event • Congestive heart failure in 30 d preoperatively • Dyspnea • Current smoker within 1 y • History of COPD • Dialysis • Acute renal failure • BMI class • CPT-specific linear risk
Outcome	Intraoperative/ postoperative MI, pulmonary edema, VT, cardiac death	MI, pulmonary edema, ventricular fibrillation, complete heart block, cardiac death	Intraoperative/ postoperative MI or cardiac arrest within 30 d	Cardiac arrest, MI, all-cause mortality within 30 d
Derivation set ROC	0.61	0.76	0.88	0.90 (cardiac arrest or MI) 0.94 (mortality)
Validation set ROC	0.701	0.806	0.874	Not reported

ASA indicates American Society of Anesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPT, Current Procedural Terminology; ENT, ear nose and throat; MI, myocardial infarction; NSQIP, National Surgical Quality Improvement Program; ROC, area under the receiver operating characteristic curve (C statistic); PAC, premature atrial contractions; PVC, premature ventricular contraction; and VT, ventricular tachycardia.

to counsel patients about the advisability of avoiding an operative procedure. The revised cardiac risk score uses six equally weighted variables to calculate risk. These include previous diagnosis of coronary artery disease, cerebral vascular disease, diabetes mellitus requiring insulin therapy, renal insufficiency, and the need for high-risk noncardiac surgery (suprainguinal vascular surgery, abdominal operations, and thoracic procedures). Ford and coauthors[4] reported a meta-analysis of available studies that assessed the accuracy of the revised cardiac risk score. The analysis showed that the revised cardiac risk score was useful for predicting perioperative cardiac complications in nonvascular, noncardiac surgical patients. The index was weaker for predicting cardiac events in vascular surgery patients. The authors hypothesized that the weaker risk prediction in vascular surgery patients may be the result of a larger impact of known coronary artery disease, which would weaken the impact of other factors such as diabetes mellitus requiring insulin therapy. The authors did not recommend using the risk score to evaluate risk in vascular surgery patients and concluded that the risk score is not a valid instrument for predicting all-cause mortality.

In an editorial that accompanied the article by Ford and colleagues, Goldman[5] stressed that the predictive value of the revised cardiac risk score in nonvascular, noncardiac surgery patients was, at the time of his publication, superior to any other available risk calculation instrument. Goldman also emphasized that validation studies of the risk calculation will consistently find scoring systems less accurate because of differences in data derived by careful history and physical examination as compared with medical record reviews. All in all, the data support the use of the revised cardiac risk score as a means of determining the need for preoperative testing. Prediction of mortality is reasonably good, so that very high-risk patients could be counseled to forego elective procedures.

Additional perspective on the use of the NSQIP risk calculator was presented in an article by Gupta and coauthors[6] in *Circulation,* 2011. The authors queried the ACS NSQIP database, which consists of nearly 212,000 patients who underwent surgical procedures. Of these patients, 1,371 developed postoperative MI and/or cardiac arrest. Logistic regression was used to develop a cardiac risk calculator using risk factors such as ASA score, age, serum creatinine level, dependent functional status, and type of operation. Assessment of the risk calculator showed that area under the receiver operating characteristic (ROC) curve for predicting postoperative MI or cardiac arrest was 0.88, which provided excellent predictive value. When the revised cardiac risk score was applied to the same cohort of patients, the area under the ROC curve was 0.74, or moderately accurate for predicting postoperative MI or cardiac arrest. The authors stated that there are strong reasons for adjusting the risk calculator according to the type of operation contemplated. For example, risk of cardiac complications after laparoscopic cholecystectomy is significantly different than the risk following pancreaticoduodenectomy. The authors also emphasized the predictive value of dependent functional status. According to the data reported, the combination of ASA score and functional status was more influential as a composite risk factor than a history of congestive cardiac failure. Gupta and colleagues also stressed that diagnosing MI using troponin assay was significantly more accurate than the diagnostic approaches used to develop the revised cardiac risk score. The authors concluded that the presented risk calculator is accurate and useful. The risk calculator is available at *www.surgicalriskcalculator.com/miorcardiacarrest*. The calculator is also available as a smartphone app.

In an editorial that accompanied the Gupta article, Grover and Edwards[7] confirmed that the risk calculator was accurate and applicable at the bedside using readily available data and handy electronic platforms. Although additional research will assist in providing validation of this model, it is sufficiently accurate to be incorporated into current practice.

One important benefit of accurate risk prediction is the provision of support for the decision to use or omit extensive preoperative cardiac testing (stress tests, coronary angiography) for patients who are contemplating elective operations. Current data suggest that preoperative testing is overused. This topic was addressed in an opinion piece by Chopra and coauthors[8] in *Annals of Internal Medicine,* 2010. The authors stated that unnecessary preoperative cardiac testing is a significant contributor to the increasing cost of health care in the United States. The most recent practice guidelines recommend preoperative testing (initially with 12-lead electrocardiography and echocardiography) for certain, clearly identified, groups. These

groups are indicated in the article (Figure 2). According to the authors, the perceived benefit of preoperatively screening stable patients for coronary artery disease, with myocardial revascularization used in patients with operable lesions, came from retrospective studies in vascular surgery patients. These studies showed that mortality risk was reduced in patients who underwent preoperative myocardial revascularization. Further analysis of these data as well as other research cited by the authors has shown that the benefit observed was restricted to patients with poor left ventricular ejection fraction and 3-vessel coronary artery disease. When data for these patients were reviewed, many of them would have been candidates for coronary revascularization because of clinical indications separate from the prospect of future noncardiac surgery. The authors cited additional data confirming that patients with stable coronary artery disease treated with optimal medical therapy derived no additional benefit from preoperative coronary artery bypass or percutaneous stenting.

Figure 2 Identification of patient groups where detailed preoperative cardiac evaluation is indicated. Reproduced from Chopra and coauthors[8] with permission.

Cardiac Conditions Warranting Evaluation, Treatment, and Testing Before Noncardiac Surgery*

Condition	Clinical Examples
Unstable coronary syndromes	Unstable angina (CCS class III or IV) Acute myocardial ischemia or infarction Recent myocardial infarction (>7 d but ≤1 mo)
Decompensated heart failure	NYHA functional class IV symptoms New-onset heart failure or newly detected heart failure Deteriorating heart failure (e.g., pulmonary edema, PND, weight gain, rales)
Significant atrial arrhythmias	Symptomatic bradycardia High-grade atrioventricular block Mobitz type II block Third-degree atrioventricular block Supraventricular arrhythmias with rapid ventricular rate at rest (≥100 beats/min) Atrial fibrillation with rapid ventricular rate at rest (≥100 beats/min)
Ventricular arrhythmias	Newly recognized or detected ventricular tachycardia Ventricular fibrillation
Severe valvular disease	Severe aortic stenosis (AVA ≤1.0 cm^2 or mean pressure gradient ≥40 mm Hg) Symptomatic mitral stenosis (associated with heart failure or presyncope)

AVA = aortic valve area; CCS = Canadian Cardiovascular Society, NYHA = New York Heart Association; PND = paroxysmal nocturnal dyspnea.
* Data are from reference 4.

Medications for Reducing Cardiac Risk

The most well-known medications used to reduce risk of cardiac events in surgical patients include aspirin, β-blocking agents, and statin drugs. Other pharmacologic agents that are important in this area include anticoagulants and antiplatelet agents. These drugs are encountered in patients who have undergone prior treatment for cardiac or vascular disease and who have indications for noncardiac surgical procedures. Successfully managing these patients requires cooperation and clear communication among surgeons, primary care providers, cardiologists, and anesthesiologists.

The practice guidelines document[1] and a summary article on the perioperative management of patients undergoing noncardiac procedures[3] recommend that patients receive perioperative aspirin therapy and this recommendation is supported by data reviewed in the guidelines document as well as in other large studies.[9] Patients who are taking β-blocking drugs should continue these drugs during the perioperative period; this recommendation is supported by strong evidence. Recommendations supported by moderate evidence are that β-blockers can be considered for patients who are at a high risk for cardiac complications (more than one risk factor) and who are contemplating vascular surgical procedures. The articles

recommended against the use of β-blockers for patients who require vascular procedures and who are at a low risk for cardiac complications (one or zero risk factors). The one exception to these recommendations would be if patients are already taking β-blockers. The potentially beneficial actions of β-blocking drugs include modulation of the catecholamine surge that accompanies anesthesia and surgical procedures with resulting improvement in myocardial oxygen delivery. Hazards of β-blocker use include bradycardia and hypotension. These factors increased the risk for complications such as stroke. These recommendations for non-use of β blocking drugs are supported by additional data reviewed in an article by Eagle and coauthors[10] in *JAMA-Internal Medicine,* 2015.

Additional perspective on the use of perioperative β-blocking agents was presented in an article by White and coauthors[11] in the *American Journal of Health System Pharmacy,* 2010. The authors conducted a systematic review of available literature. The analysis showed that patients at intermediate or low risk for perioperative cardiac complications who were not taking β-blocking agents prior to operation but were treated with these agents in the perioperative period had fewer cardiac events over short- and long-term follow-up, but the clinical and statistical significance of this risk reduction was small. The risk of dangerous hypotension and severe stroke were both significantly increased in patients treated with β-blockers.

An attempt to use data from a national database to identify high-risk patients who might benefit from perioperative β-blocking drug therapy was described in an article by Andersson and coauthors[12] in *JAMA-Internal Medicine,* 2014. The authors analyzed data from national registries in Denmark including outcomes data from nearly 29,000 patients. The data analysis showed that significant benefit from perioperative β-blocker therapy was only observed in patients who had significant heart failure and/or a history of MI in the 3–6 months prior to the planned operative procedure. The data support the conclusion that careful clinical judgment needs to be used in formulating the decision to use perioperative β-blocker therapy.

Statins represent another group of drugs that might reduce the risk of postoperative cardiac events. The practice guidelines document discussed earlier recommends that statin use be continued in the perioperative period for patients who are taking these drugs. This recommendation is supported by strong evidence. The guidelines recommend that statins be considered for patients undergoing vascular operations regardless of risk status. Statins should be considered in patients with one cardiac risk factor who are to undergo intermediate-risk noncardiac operations. Potentially beneficial actions of statins include stabilization of atherosclerotic plaques, improved endothelial function, and reduced vascular inflammation.

A meta-analysis that assessed the effect of statin use on postoperative MI, atrial fibrillation, and length of stay was by Chopra and coauthors[13] in *Archives of Surgery,* 2012. The meta-analysis was performed using rigorously applied standard techniques. Prospective trials involving more than 2,200 patients were included. The analysis showed that statin-naïve patients who were treated with these drugs beginning prior to operation had significant reductions in the risk of MI, atrial fibrillation, and hospital length of stay. The reduction in the risk of atrial fibrillation was restricted to patients undergoing cardiac procedures. There was a trend toward reduction in mortality risk, but this did not reach statistical significance. The authors concluded that statin therapy is indicated in statin-naïve patients who are to undergo cardiac, major vascular, and possibly other high-risk procedures.

In an invited critique that accompanied the article, Dr. David Spain cautioned that the data used to support the conclusion came primarily from trials conducted in cardiac surgery patients. He agreed, however, with the conclusion that patients at increased risk for cardiac complications and patients undergoing high-risk procedures should be considered for statin therapy.

An article that analyzed data from a large clinical database of patients who underwent noncardiac procedures following placement of a coronary artery stent was by Hawn and coauthors[14] in *JAMA,* 2013. The authors averred that current recommendations for management of patients with drug-eluting stents who require noncardiac surgery state that surgery should be delayed for one year following stent placement. In this report, the authors queried a large Veterans Health Administration services database; outcomes data on nearly 125,000 patients were analyzed. The authors found that the risk of significant postoperative coronary events increased in patients who underwent emergency operations and in patients with very severe cardiac disease. The risk of postoperative events stabilized at six months after stent insertion. The authors concluded that recommendations

for delaying needed operative procedures for one year after stent placement should be reevaluated. The message for surgeons caring for patients who need surgery following stent placement was clearly articulated in an editorial by Brilakis and Banerjee[15] that accompanied the article by Hawn. The authors confirmed that available data support the conclusion that needed surgery can be performed in patients within six weeks of placement of a bare metal stent and after six months in patients who have drug-eluting stents. Continuation of dual antiplatelet therapy is safe in the perioperative period in patients with low or moderate bleeding risk. Bridging therapy with low-molecular weight heparin should be avoided[16] in patients with coronary artery stents and the use of glycoprotein IIb or IIIa inhibitors (for example, cangrelor) should be considered beginning in the first postoperative day in patients who require operation within the first 60 days after placement of a bare metal stent, since the highest risk of stent thrombosis is during the first postoperative day.

Baron and coauthors[17] reviewed the management of patients who present for major noncardiac operations while on anticoagulant or antiplatelet drugs in the *New England Journal of Medicine,* 2013. This article is supplied as a full-text reprint accompanying some formats of *SRGS*. Each year, 10% of patients on antithrombotic drug therapy will require a procedure that interrupts this antithrombotic therapy. The decision to continue antithrombotic therapy or interrupt the therapy and use bridging anticoagulant strategies requires cooperation and good communication between the provider who manages antithrombotic therapy and the surgeon who will perform the needed procedure. The desirable pathway is clear for patients at low risk for perioperative bleeding and at high risk for a thromboembolic complication—continue antithrombotic drug therapy. Similarly, patients at high risk of perioperative bleeding and low risk for a thromboembolic complication should have antithrombotic therapy interrupted and bridging anticoagulation instituted. The authors acknowledged that decisions regarding the management of patients in moderate risk categories are challenging and that data to support these decisions are lacking. Perioperative risk of thrombotic complications (stroke) in patients with atrial fibrillation can be estimated with available scoring systems that award points for risk factors such as congestive heart failure, age >75 years, history of prior stroke or transient ischemic attack, and diabetes. Risk scores of 1 or 2 are associated with minimal risk and interruption of antithrombotic therapy with bridging anticoagulation should be safe. Patients with scores of 3 or higher represent a high-risk group. The authors indicated that risk of thromboembolic complications in patients with cardiac valvular disease varies depending on the number of valves involved and associated factors such as atrial fibrillation and congestive heart failure.

Baron and coauthors observed that data to support an informed decision on whether to use bridging therapy with heparin vs. continuation of anticoagulation with warfarin are scarce. Periprocedural thromboembolic events occur in 1%–3% of patients given bridging therapy during an 8-day interruption of warfarin according to data cited by the authors. Significant bleeding complications also occur. Data from a trial of bridging heparin therapy cited by the authors indicate a 16% rate of significant wound-site hematoma in patients treated with bridging therapy. The authors presented their approach to the use of bridging therapy for patients who are receiving chronic warfarin therapy. They recommended that bridging therapy with therapeutic doses of unfractionated heparin be used in patients with impaired renal function. For other patient groups deemed to be at high risk of bleeding with continued warfarin therapy, they recommended therapeutic doses of low-molecular-weight heparin (enoxaparin). Their protocol includes stoppage of warfarin five days before the planned procedure, with institution of bridging heparin therapy when the INR falls below the therapeutic range. The final bridging therapy dose is given 24 hours before the planned procedure. After the procedure is complete, they recommend rechecking the INR and restarting warfarin if hemostasis is secure. As an alternative, bridging heparin therapy can be restarted along with warfarin 48 hours after the procedure (72 hours after endoscopic sphincterotomy) and continued until the INR is in the therapeutic range. The approach to bridging therapy recommended by the authors is presented in a table (Figure 3). The authors provided helpful reviews of newer anticoagulant and antiplatelet drugs, and protocols for emergency reversal of anticoagulant effects. Readers are encouraged to review the full article for the recommended approaches and for explanations of available supporting data.

Figure 3 Suggested approach to bridging heparin therapy for patients on chronic anticoagulant therapy. Reproduced from Baron and coauthors[17] with permission.

Approach to Bridging Therapy.

Condition	Bridging Therapy Required	No Bridging Therapy	Comments
Mechanical heart valve	Mitral-valve replacement, two or more mechanical valves, non-bileaflet aortic-valve replacement, or aortic-valve replacement with other risk factors	Aortic-valve replacement, bileaflet prosthesis, and no additional risk factors	Other risk factors include prior stroke, TIA, intracardiac thrombus, or cardioembolic event
Nonvalvular atrial fibrillation	Prior stroke or embolic event, cardiac thrombus, or $CHADS_2$ score of ≥4	No prior stroke or embolic event, absence of cardiac thrombus, or $CHADS_2$ score of <4	Prior stroke, TIA, intracardiac thrombus, or cardioembolic event increases risk
Venous thromboembolism	Venous thromboembolism within previous 3 mo or severe thrombophilia	Venous thromboembolism >3 mo previously or no additional risk factors (e.g., active cancer and nonsevere thrombophilia)	Consider inferior vena cava filter if venous thromboembolism occurred <1 mo previously, if urgent or emergency surgery is required, or if there is a contraindication to anticoagulation therapy

Editorial Comment

There is convincing evidence to support careful preoperative cardiac risk assessment. Furthermore, it is expected that an increasing number of patients will present for operation already taking β-blocking drugs, statins, or both. In this case, drug therapy with both drugs should be continued during and after the perioperative period with the dose or type of drug adjusted to make certain that the full effects of both drugs are maintained. For intermediate-risk patients undergoing high-risk operations (abdominal or thoracic vascular procedures) and for patients with an estimated risk of a postoperative cardiac complication of 1% or higher, β-blocking drug therapy, at least, should be implemented and dosage adjusted progressively during the preoperative interval to obtain a resting heart rate in the 55–65 bpm range. Therapy should continue into the postoperative recovery period. Other adjuncts, such as regional anesthesia/analgesia, aspirin therapy, and statin therapy, may be useful.

For patients undergoing anticoagulant therapy because of significant risk of thromboembolic complications, continuation of warfarin or bridging therapy with heparin can be chosen based on risk analysis. In patients with recent placement of a coronary artery stent, delay of a surgical procedure based on the type of stent placed should be considered.

Epidemiology & Diagnosis of Perioperative Myocardial Infarction

Devereaux and coauthors[18] stated that, worldwide, more than 200 million patients undergo noncardiac surgical procedures annually. In their article in *Annals of Internal Medicine,* 2011, the authors cited data from a large prospective trial they conducted indicating that postoperative MI is diagnosed in 5% of patients after noncardiac surgical procedures. The authors reviewed data on more than 8,000 patients enrolled in a randomized prospective trial of β-blocker therapy before and after noncardiac surgery. Of the patients diagnosed with postoperative MI, 74% had clinical evidence of infarction within 48 hours of operation. Two-thirds of patients diagnosed with MI were asymptomatic; the diagnosis was made on the basis of elevation of troponin or CPK-MB levels. Biomarker elevations of more than 3.6 times the normal serum level of the marker chosen were considered an independent predictor of 30-day mortality. Electrocardiographic evidence of MI was significantly different from changes seen in spontaneous MI, in that most perioperative infarcts demonstrated ST segment depression or T-wave inversion rather than ST segment elevation. Because of the lack of typical ischemic symptoms and typical electrocardiographic changes, the authors recommended cardiac biomarker monitoring, especially in the early postoperative period. The data showed that risk of 30-day mortality

was significantly increased in patients who developed MI during the postoperative interval. The authors identified older age, need for vascular surgery, need for urgent or emergency surgery, significant postoperative bleeding, serum creatinine level >2 mg/dL, and sustained increases in heart rate of more than 10 beats/minute as risk factors for MI. Based on the cardiac risk calculator described by Gupta and coauthors,[6] an estimated risk of postoperative cardiac event of 0.75% or higher would suggest the need for postoperative monitoring of cardiac biomarkers.

Confirmation of the association of postoperative cardiac biomarker elevations with postoperative mortality risk was in an article by Redfern and coauthors[19] in *Anesthesia,* 2011. The authors conducted a meta-analysis using conventional techniques to assess the impact of a postoperative "troponin leak," defined as an elevation of troponin below the level that would confirm a diagnosis of myocardial infarction. Nine studies were included in the analysis and all patients underwent vascular procedures. Troponin levels were monitored postoperatively in all patients. Elevation of serum troponin levels below the level that would indicate significant myocardial infarction was associated with a fivefold increase in risk of 30-day and 180-day mortality. The authors hypothesized that inflammation and leucocyte infiltration of the coronary microcirculation could be the cause of the "troponin leak." The authors recommended that troponin monitoring be considered in all patients undergoing vascular operations. Although this analysis was limited because risk factors other than a vascular operation (elevated creatinine, advanced age) were not reported, the data suggested that troponin monitoring could be beneficial in selected high-risk patient groups.

Another article by Devereaux and coauthors[20] in *JAMA,* 2012, presented outcomes data on more than 15,000 patients who underwent noncardiac surgical procedures and were enrolled in a prospective randomized trial. Postoperative fourth-generation troponin levels were monitored in all patients. The authors' analysis showed that elevations of fourth-generation troponin to a level of 0.02 ng/mL or higher (diagnostic threshold for myocardial infarction is 0.04 ng/mL) was associated with a significant risk of 30-day mortality. The authors stressed that fourth-generation troponin is specific for myocardial tissue. The strong association of low levels of the biomarker with mortality risk suggested that efforts to modify this risk are indicated. The authors pointed out that available data suggest that treatment of this patient group with aspirin and statin drugs could modify the elevated mortality risk.

An article that reviewed data on risk factors for MI following colorectal procedures was by Moghadamyeghaneh and coauthors[21] in the *American Surgeon,* 2015. This article is supplied as a full-text reprint accompanying some formats of *SRGS*. The authors reviewed data on nearly 2.5 million patients in the National Inpatient Sample. Postoperative MI occurred in 1.5% of patients undergoing colorectal procedures, but postoperative mortality occurred in nearly 30% of this patient group. Risk for MI was highest in patients with a history of congestive heart failure and/or chronic renal insufficiency.

Additional perspective on risk factors for perioperative MI was presented in an article by Causey and coauthors[22] in the *Journal of Surgical Research,* 2011. The authors conducted a retrospective single-center study of patients undergoing colon and rectal operations over an 8-year interval. Data from 339 patients were presented. The authors found that preoperative hypotension (systolic blood pressure <90 mm Hg), elevation of serum creatinine, and dependent functional status were predictive of perioperative MI.

The possibility exists that the process of preoperative evaluation and preparation might yield information leading to preventive measures that could reduce the risk of subsequent cardiac events. This topic was the focus of an article by McFarlane and coauthors[23] in *Anesthesia,* 2012. The authors queried a large government administrative database in Scotland and were able to obtain outcomes data on 183,500 patients who had no prior hospital admission for cardiac disease; these patients were 50–75 years old and underwent low- to moderate-risk noncardiac operations. The analysis showed significant reduction in the risk of all-cause mortality and the rate of subsequent cardiac events over a 3-year follow-up interval in patients who underwent a surgical procedure. The authors acknowledged that the study is limited because the baseline health of the two cohorts, aside from the fact that there were no prior hospital admissions for a cardiac diagnosis, is unknown. Patients who underwent operation may have been healthier than the control cohort. On the other hand,

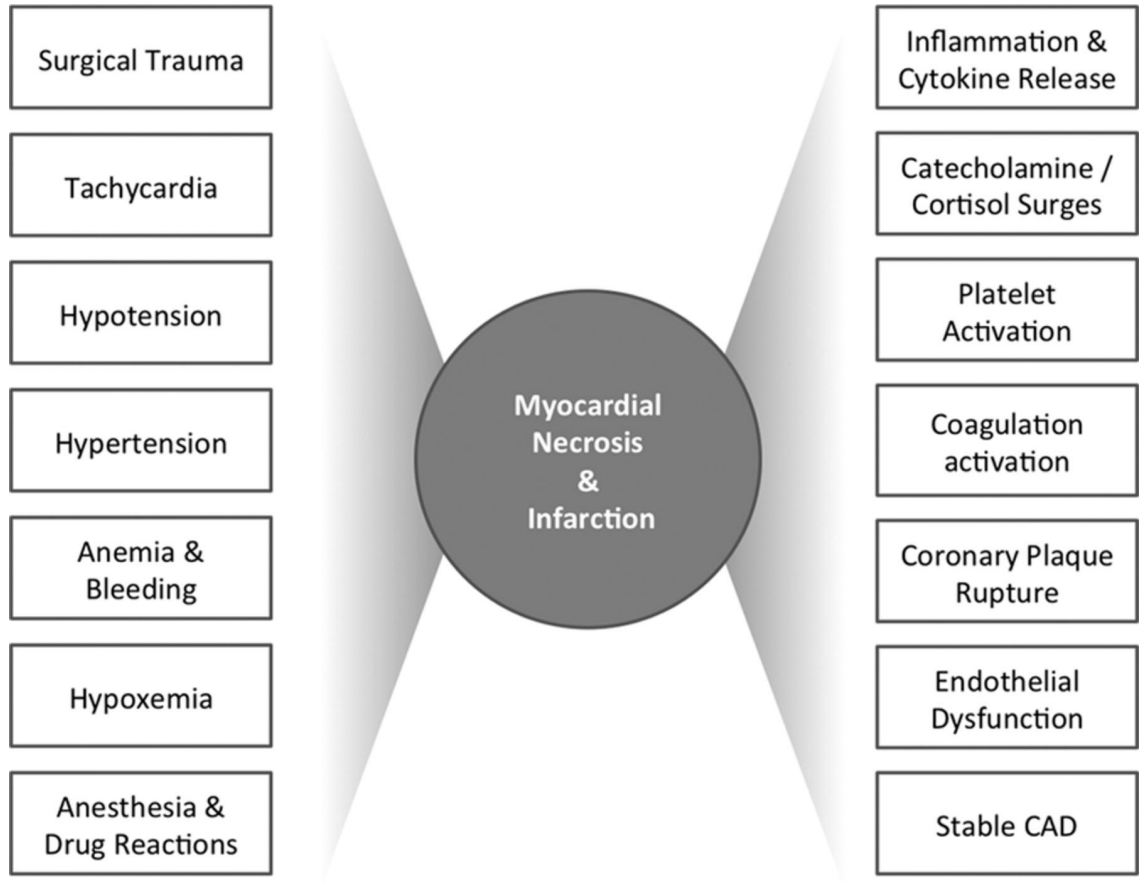
evaluation for operation may have prompted advice on lifestyle changes and other health interventions that led to risk reduction in the patients who had surgery. It is clear that preoperative evaluation offers an opportunity for patient education that could be used to modify risk of subsequent morbidity.

Pathophysiology of Myocardial Infarction

Postoperative cardiovascular events do not have a single cause. Multiple factors, including anesthesia-related hypotension, the perioperative inflammatory response, perioperative activation of the coagulation mechanism, and factors related to preexisting cardiovascular disease, contribute to the development of these complications. The article by Smilowitz and Berger[3] contains a useful illustration of the various contributing factors (Figure 4).

A review of the pathophysiology of perioperative MI was by Biccard and Rodseth[24] in *Anesthesia,* 2010. The authors indicated that perioperative MI is a significantly different entity than MIs observed in nonsurgical populations. In nonsurgical patients, 70% of the MIs are the result of coronary artery plaque rupture. In the remaining 30%, there is evidence of conditions contributing to plaque instability. By contrast, plaque rupture is identified in only 7% of patients who die of postoperative MI and are examined at autopsy. Most patients who have a postoperative MI are clustered in the first 3–4 days after an operation, where evidence of imbalance of myocardial oxygen supply and demand is commonly found. The patients with evidence of plaque rupture, by comparison, had the onset of clinical signs of MI that was evenly distributed over the first two postoperative weeks.

Figure 4 Factors contributing to the pathophysiology of postoperative cardiac events. Reproduced from Smilowitz and Berger[3] with permission.



Postmortem studies cited by the authors indicated that early postoperative MI occurs most commonly in patients found to have three-vessel coronary artery atherosclerosis at autopsy. Coronary artery thrombosis occurs in the diseased vessels but is not associated with findings of plaque rupture. Additional data cited by the authors indicated that although coronary thrombosis occurs in diseased coronary arteries in patients who die from postoperative MI, total coronary artery occlusion is found in only 19% of these patients. This suggests that an imbalance in myocardial oxygen delivery and oxygen demand contribute to fatal myocardial infarction in a significant number of patients. Nonocclusive thrombosis caused by postoperative inflammation, endothelial dysfunction, and hypercoagulability are likely to be important contributors to nonocclusive thrombus formation.

The authors cited data from studies of patients who underwent preoperative coronary angiography that showed a strong association between preoperative coronary atherosclerosis and subsequent MI. Of interest is that the presence of coronary artery collateral channels did not protect against postoperative MI. Additional data indicated that postoperative MI occurs in myocardium supplied by a stenotic coronary artery in only 50% of patients who had tests to determine areas of inducible ischemia preoperatively. This finding suggests that a diffuse process (myocardial oxygen supply-demand imbalance) contributes significantly to the factors that cause postoperative MI. When data on the association of postoperative MI with sustained tachycardia are considered, the proposed oxygen supply-demand imbalance hypothesis is strengthened.

Perioperative Cardiac Arrhythmias

Earlier in this issue, the association between postoperative inflammation, postoperative tachycardia, and postoperative atrial fibrillation with cardiac morbidity was discussed. In patients at high risk for perioperative cardiac events, control of heart rate and rapid diagnosis and therapy for a treatable tachycardia are important for prevention of cardiac complications. The most common treatable tachycardia encountered in postoperative patients are supraventricular tachycardia and atrial flutter/fibrillation. In this section, we will review pertinent features of the diagnosis and management of these cardiac rhythm disorders.

Management of Supraventricular Tachycardia & Atrial Fibrillation

Supraventricular tachycardia is the subject of an older but still relevant review by Fox and coauthors[25] in *Mayo Clinic Proceedings*, 2008. The authors provided a working definition of supraventricular tachycardia, which includes all tachycardia arising cephalad to the bifurcation of the bundle of His and all tachycardia dependent on the bundle of His for impulse transmission. These tachycardia usually have rates exceeding 100 bpm (unless atrioventricular conduction block is present) and QRS morphology is usually normal. In the presence of bundle branch block, however, QRS complexes might be widened or otherwise abnormal in shape. Data from long-term ambulatory electrocardiographic monitoring has permitted estimates of the incidence of supraventricular tachycardia. The authors cited data that disclosed an incidence of 76% in a group of elderly patients with a 20% incidence of symptomatic coronary artery disease. In studies of asymptomatic healthy patients who are between 18 and 65 years old, the incidence ranged from 12% to 18%.

Supraventricular tachycardia is usually of sudden onset and may spontaneously terminate. The patient may complain of chest pain and syncope occasionally occurs (usually in very rapid tachycardias associated with reductions in cardiac output). Although no clear association between chest pain during a tachycardia episode and coronary artery disease has been established, the diagnosis may be suspected in elderly patients with tachycardia and chest pain. Patients usually complain of palpitations. Patients with chronic heart failure may not sense the palpitations but, instead, present with cardiac decompensation. The catecholamine response stimulated by tachycardia and hypotension serves to perpetuate the rhythm disturbance.

The authors stated that atrioventricular nodal re-entry, atypical atrioventricular nodal re-entry, or atrial tachycardia, are the usual mechanisms of these rhythm disturbances. Tachycardia that are atrioventricular node dependent are usually terminated by inducing atrioventricular nodal block with a vagal stimulating maneuver

(the Valsalva maneuver, carotid sinus massage, or immersion of the face in cold water). Atrioventricular node independent rhythms include atrial flutter and atrial fibrillation.

Tachycardia diagnosis is usually possible using a 12-lead electrocardiogram, which is preferred over a rhythm strip. QRS morphology is usually normal with QRS duration of 90 milliseconds or less. QRS complexes might be abnormal if there is intermittent or permanent bundle branch block. Other factors to be considered in interpreting the electrocardiogram are the heart rate, mode of onset and termination of the tachycardia, relative position of the P wave within the RR interval, and morphology of the P wave. The tachycardia rate is usually higher than 100 bpm and might be variable. A steady rate of 150 bpm suggests atrial flutter with a 2:1 atrioventricular block, according to Fox and associates.[25]

Another means of determining the type of tachycardia is by examining the relationship of the P wave to the preceding and subsequent R wave. When the distance between the R wave and the next P wave is longer than the subsequent PR interval, the tachycardia is a "long RP" rhythm. If the distance between the R wave and the subsequent P wave is shorter than the subsequent PR interval, the rhythm is termed "short RP." A long RP tachycardia is atrial and might progress to flutter or fibrillation. Supraventricular tachycardia, according to the authors, are mainly short RP rhythms. At very rapid heart rates, RP and PR intervals become very short and might be difficult to interpret.

Management of supraventricular tachycardia is usually straightforward because the patients are usually hemodynamically stable. If there is instability, the patient is managed according to the typical ABC approach emphasizing airway, breathing, and circulation. Vagal maneuvers such as carotid sinus massage may terminate the rhythm promptly and these maneuvers are ineffective in atrial flutter/fibrillation. Carotid sinus massage should not be done if there is a carotid bruit present. Pharmacologic management of supraventricular tachycardia is accomplished using adenosine, calcium channel blockers, or β-blocking drugs. Adenosine is the first-line drug and is given in 6 mg or 12 mg boluses. Smaller doses are used in patients taking dipyridamole.

Broadening of the QRS complex might occur in supraventricular tachycardia if there is bundle branch block. Fox and colleagues cautioned that if the patient is older than 70 and/or there is a history of symptomatic coronary artery disease, a broad QRS tachycardia should be considered a ventricular tachycardia until proved otherwise. An article that discussed the use of response to adenosine bolus therapy as a means of differentiating supraventricular from ventricular tachycardia when wide QRS tachycardia is encountered was in *Critical Care Medicine*, 2009.[26] The authors pointed out that differentiation of atrial from ventricular tachycardia when the heart rate is steady and the QRS complex is widened is important, but current algorithms are neither sensitive nor specific in identifying the type of rhythm that is present. Drug therapy using procainamide or amiodarone might effectively treat the rhythm, but side effects such as hypotension limit the usefulness of these agents. While electrical cardioversion is effective, it is painful, does not protect against recurrence of the rhythm, and offers little diagnostic information.

The authors hypothesized that adenosine would safely terminate most supraventricular tachycardias, would slow heart rate enough to allow detection of atrial flutter or fibrillation, and would not predictably alter ventricular tachycardia. Over a 15-year interval, the authors treated 197 patients with steady-rate wide QRS complex tachycardia with a 12-mg bolus of adenosine. Patients determined to have ventricular tachycardia were older and more often had a history of MI and prior episodes of ventricular tachycardia. Two of 81 patients with ventricular tachycardia responded to adenosine, while 104 of 116 patients with nonventricular tachycardia responded to adenosine. There were no serious adverse events (defined as emergent drug therapy or electrical shock) observed in either subgroup. The authors concluded that nonresponse to adenosine was the only factor that diagnosed ventricular tachycardia with a high sensitivity and specificity.

Of the atrial arrhythmias, atrial fibrillation is the most commonly encountered. Siu and coauthors[27] discussed the management of acute atrial fibrillation in *Critical Care Medicine*, 2009. The authors reported a randomized, nonblinded trial comparing the effectiveness of diltiazem, digoxin, and amiodarone for rate control and symptom improvement in patients presenting acutely with symptomatic, new-onset atrial fibrillation. The authors

stated that atrial fibrillation is a common arrhythmia and the frequency of this condition is increasing. Traditionally, two approaches have been used to manage atrial fibrillation, rhythm control, and rate control. Of note is that a recent randomized, prospective trial of managing postoperative atrial fibrillation in cardiac surgery patients showed no distinct advantage to using either a rate control or a rhythm control approach.[28] The choice of approach can be made based on available expertise and equipment. Siu and coauthors[27] indicated that rhythm control approaches use direct-current cardioversion. They also pointed out that this modality may not be readily available. The authors stressed that guidelines published from the American Heart Association recommended emergency direct-current cardioversion only for patients with acute atrial fibrillation who are hemodynamically unstable. Direct current cardioversion may require that the patient be anticoagulated, especially if there is atrial enlargement. This fact limits application of this modality to postoperative patients. The authors analyzed results in 166 patients. Patients were excluded from the study if they were unstable, had evidence of symptomatic coronary artery disease, were hypotensive, had an implanted defibrillator, had a history of recent MI, had a history of heart failure, or had angina pectoris. Drug therapies utilized were diltiazem, digoxin, and amiodarone. The endpoints examined were control of rate (heart rate <90 bpm, sustained, at 24 hours following initiation of therapy) and improvement of symptoms. In this study, rate control and symptom improvement was best achieved with diltiazem. There was only one adverse event recorded, an episode of phlebitis at the injection site, in one of the patients receiving amiodarone.

In an editorial that accompanied the Siu article, Karth[29] stressed that these data, though valuable and convincing, were obtained in relatively healthy patients and, because of this, the data might not be directly applicable to typical postoperative patients, since surgical patients are increasingly presenting with significant comorbid conditions. Nonetheless, there is sufficient reason, based on the data reported by Siu, to consider diltiazem as an initial therapy for patients with acute, new-onset atrial fibrillation when rhythm control strategies are not appropriate.

In surgical patients, prevention of postoperative atrial fibrillation would be desirable if risk could be quantified and if safe, pharmacologic prevention strategies were available. A prevention strategy was discussed in a report by Zebis and coauthors[30] in *Annals of Thoracic Surgery*, 2007. The authors reported a randomized, placebo-controlled, double-blind trial comparing amiodarone with a placebo in a group of patients undergoing coronary artery bypass (a known high-risk group for the development of postoperative atrial fibrillation). The authors observed a 14% absolute risk reduction for patients treated prophylactically with amiodarone. Of the patients in the placebo group who developed atrial fibrillation, more than 80% were symptomatic, while just over 40% of the patients in the amiodarone group who developed atrial fibrillation were symptomatic. While these data have limited application to typical general surgery patients, a preventive strategy might be considered in patients who have previously undergone cardioversion for atrial fibrillation if antiarrhythmia drugs are not already in use.

Cardiac Failure in the Surgical Patient

Cardiac failure is an extremely common medical problem. More than one million hospitalizations annually in the United States are for cardiac failure and there is a 50% likelihood of death or recurrence of cardiac failure during the six months subsequent to a hospital admission. Cardiac failure will develop in up to one-third of patients with symptomatic ischemic cardiac disease; this condition will develop in 15% of diabetics and 10% of patients with hypertension. While it is unlikely that surgeons will be involved in the first-line management of patients with acutely decompensated cardiac failure, surgeons will be called upon to assist in the care of patients with heart failure who develop conditions requiring elective or urgent surgical procedures. It is important that surgeons understand the fundamentals of disordered cardiac function characteristic of the various forms of heart failure as well as the pharmacology and side effects of the various therapies employed in these patients.

Management of Heart Failure in the Surgical Patient

Preoperative cardiac failure is known to be associated with a significant increased risk for postoperative cardiovascular events.[31] When postoperative cardiac failure is suspected, history, physical examination, and acute echocardiographic imaging are used to establish a diagnosis. Laboratory studies, including serum assays of brain natriuretic peptide (BNP) or N-terminal pro-Brain natriuretic peptide (NT-proBNP) might be helpful in providing additional diagnostic information. The use of these serum markers was discussed in an older article by Omland[32] in *Critical Care Medicine*, 2008. Omland stressed that important, incremental diagnostic information can be gained by obtaining serum levels of BNP or NT-proBNP in the emergency department/ICU in patients presenting with acute dyspnea. In several studies cited by the author, abnormal BNP or NT-proBNP was 84%–90% accurate in diagnosing diastolic cardiac failure as the cause of acute dyspnea. Omland stressed that BNP levels may be normal in patients with chronic heart failure. Furthermore, BNP and NT-proBNP levels were not consistently useful as means of assessing progression or improvement of cardiac failure.

Therapy for systolic cardiac failure depends on the clinical presentation. The presence of echocardiographic evidence of increased filling pressures suggests the use of loop diuretics (furosemide) to improve pulmonary congestion, dyspnea, and hypoxia. Significant low cardiac output states in patients with systolic cardiac failure can be treated with afterload reduction using vasodilators. Sublingual nitroglycerin is the first-line approach in this regard. With very low cardiac output, short duration inotropic therapy can be considered. Petersen and Felker[33] reviewed the use of inotropic drugs for systolic cardiac failure in *Critical Care Medicine*, 2008. The authors cited data indicating a lack of clinical value of inotropic drugs in patients without clearly documented end-organ hypoperfusion. They also acknowledged the clinical challenges in documenting end-organ hypoperfusion. Traditionally, this diagnosis has been made by documenting worsening renal function. Petersen and Felker stated that increases in serum creatinine following the institution of loop diuretic therapy might indicate the presence of cardiorenal syndrome and not end-organ hypoperfusion; some patients with very low cardiac output states will maintain normal levels of serum creatinine. These patients will frequently have nonspecific symptoms such as abdominal pain, nausea, fatigue, and diminished cognitive function. Documentation of low cardiac output with echocardiography or pulmonary artery catheter monitoring will likely provide confirmatory evidence. The authors observed that documented low cardiac output in patients with systolic heart failure is a marker for increased short-term mortality. If inotropic therapy is contemplated, dobutamine and milrinone are the first-line drugs. Both drugs produce improvements in cardiac output via augmentation of cellular cyclic AMP. Milrinone has greater vasodilating function than dobutamine and might have a lower risk of inciting arrhythmias. Devices useful for supporting cardiac function include the intraaortic balloon pump, left ventricular assist devices, and ultrafiltration devices. These devices reliably support cardiac function until definitive therapies using revascularization or transplantation can be organized and implemented. These devices were discussed by Kale and Fang[34] in *Critical Care Medicine*, 2008.

According to Kumar and coauthors,[35] treatment of acute pulmonary edema (the main clinical manifestation of diastolic cardiac failure) focuses on improving oxygenation and relieving patient symptoms. Noninvasive ventilation with continuous positive airway pressure is valuable for reversing hypoxia. Early administration of a loop diuretic along with intravenous β-blocking drugs will improve pulmonary congestion, lower blood pressure and heart rate, and relieve patient symptoms. The authors stressed that diuretic-naïve patients may have a very brisk diuresis and, therefore, lower diuretic doses initially may provide a greater margin of safety. Morphine is helpful for relieving symptoms and afterload reduction with sublingual nitrate drugs is frequently helpful as well.

Editorial Comment

It seems clear that we have the capability to predict perioperative cardiac complications using global risk factors that overcome, at least partially, the imprecision associated with the use of risk-scoring systems that focus on risk factors specific to the cardiovascular system.

Perioperative MI is a potentially lethal complication occurring as a result of coronary artery plaque instability or rupture with coronary artery thrombosis. Predicting which plaque will rupture is not possible currently. Because of this, planning preoperative revascularization interventions based on identification of a "culprit" coronary stenosis does not reliably reduce the risk of perioperative MI. Indications for preoperative coronary imaging and revascularization are made based on conventional indications and these are undertaken in patients with "unstable" ischemic diseases such as unstable angina, recent MI, and cardiac failure. The usual diagnostic clues for diagnosis of MI (chest pain, Q waves or ST segment elevation on electrocardiogram, and elevated troponin levels) lack specificity in the patient who has recently undergone a surgical procedure.

Clinical signs of perioperative MI might be vague and include intermittent hypotension, changing mental status, new onset arrhythmia, and ST segment depression on electrocardiographic tracings. Because of these facts, a low threshold for use of serial troponin levels, continuous electrocardiographic monitoring, and echocardiographic imaging is necessary in order to make a prompt diagnosis.

Perioperative tachycardia will occasionally require pharmacologic intervention or even electrical cardioversion. Knowledge of the elements of diagnosis and emergency treatment of these arrhythmias will be valuable. Even though surgeons will not normally be the lead caregivers in patients with cardiac failure, it is useful to understand the pathophysiology of this condition so that factors that increase cardiac stress can be minimized during the perioperative interval. Echocardiography is the most useful modality for quantification of the severity of cardiac failure.

Cardiac Arrest & Cardiopulmonary Resuscitation

Kazaure and coauthors[36] provided data on the clinical features of cardiac arrest in surgical patients in *JAMA Surgery,* 2013. The authors cited data suggesting that 200,000–750,000 episodes of cardiac arrest occur in patients hospitalized in the United States annually. Additional data suggest that some of these incidents could be prevented because prearrest clinical events such as hypotension, sepsis, and renal failure are documented in up to 14% of patients who sustain cardiac arrest. The authors affirmed that cardiac arrest survival rates were reported mostly in hospitalized surgical patients prior to the development of closed chest cardiopulmonary resuscitation (CPR). With the advent of CPR and the dissemination of CPR training, survivors of out-of-hospital cardiac arrest were reported. Overall, however, survival rates from out-of-hospital cardiac arrest have remained at 15%–18%.

Kazaure and colleagues queried the ACS NSQIP® database to document the frequency of cardiac arrest in surgical patients and to define outcomes of CPR in this patient group. They reported outcomes data on nearly 6,400 patients. Eighty-five percent of cardiac arrests occurred postoperatively and nearly half of these events occurred in the 5-day interval following the surgical procedure. The prevalence of cardiac arrest was 1 out of 203 surgical procedures. Prevalence varied by type of surgery (1 out of 33 for cardiac procedures and 1 out of 258 for general surgery procedures). Of note is that a postoperative complication became clinically evident in 75% of patients on or before the day of the cardiac arrest. Complications included bleeding, ventilator dependence, sepsis, and renal impairment. Survival to hospital discharge was documented in 19.2% of patients. Risk factors for mortality were older age, number of comorbidities, and organ failure.

The authors stressed that all of the reported patients underwent elective operations. Cardiac arrest events occurring after elective operation are potentially preventable if the risk factors are assessed and complications leading to cardiac arrest are recognized promptly and treated ag-

gressively. A critique of this article was published in the same issue of *JAMA Surgery*. The editorialist, Dr. Michael Zenilman, pointed out that the problem of "failure to rescue" has been identified as a contributing factor to adverse outcomes of surgery. He emphasized the need to identify complications early and treat them aggressively. He also acknowledged the importance of preoperative counseling of patients, families, and caregivers so that patients near the end of life can be informed of possible outcomes of an operation so that an operation may not be a patient's preferred therapeutic approach. When an operation is chosen, patients, families, and caregivers need to understand the necessity of aggressive management of complications, even in high-risk patients. The data reported in this article are valuable. Interpretation is limited by the fact that the only outcome reported is mortality. The proportion of survivors who were neurologically disabled after CPR is unknown.

Data on the frequency of out-of-hospital and in-hospital cardiac arrest were presented in articles by Ramsay and Maxwell[37] and Ehlenbach and coauthors.[38] These articles confirmed that there are more than 400,000 sudden deaths annually ascribed to cardiac disease resulting in cardiac arrest. Ramsay and Maxwell cited data indicating 165,000 witnessed episodes of out-of-hospital cardiac arrest in the United States each year. In-hospital cardiac arrest occurs at a rate of nearly 3 events per 1,000 admissions, according to data cited by Ehlenbach and coauthors. Despite the availability of effective methods of cardiopulmonary resuscitation, mortality for witnessed out-of-hospital and in-hospital cardiac arrest exceeds 80%. All of the authors cited the disappointing statistic that nearly three-quarters of the patients who sustain witnessed, out-of-hospital cardiac arrest have no attempt at resuscitation made.

History of Cardiopulmonary Resuscitation

Ramsay and Maxwell observed that descriptions of mouth-to-mouth rescue breathing appear in the Old Testament. In the 14th century, rescue breaths were administered using bellows devices placed intranasally or through a reed inserted into the trachea via an anterior neck incision. During the 18th and 19th centuries, "humane societies" were formed in several European countries to foster the use of artificial respiration techniques for drowning victims. In studies on animals, John Hunter noted that cessation of breathing led to cardiac standstill and immediate resumption of breathing led to restoration of cardiac action. The use of electricity for defibrillation was championed by Wiggers, who also supported the use of open cardiac massage. Open massage was used for resuscitation of intraoperative cardiac arrest by Beck at the Johns Hopkins University School of Medicine and this method of resuscitation was the focus of his research from 1920 to 1937. Closed chest massage was developed at Johns Hopkins and described in a 1960 publication in the *Journal of the American Medical Association* by Kouwenhoven, Knickerbocker, and a surgeon, James Jude.[39] This article described the experimental work that was the basis for clinical application of closed chest cardiac compressions as a means of restoring circulation. The article by Kouwenhoven and colleagues concluded with the description of four patients who were successfully resuscitated using closed chest techniques. Training in techniques of cardiopulmonary resuscitation for emergency medical services personnel as well as citizen responders was made simpler and more effective by the development of life-like mannequins for intubation and resuscitation by Safar and Laerdal. Currently, national standards for citizen, emergency medical services, and in-hospital cardiopulmonary resuscitation are promulgated by courses sponsored by the American Heart Association (Basic Life Support and Advanced Cardiovascular Life Support).

Current Practice & Outcomes of Cardiopulmonary Resuscitation

Updated practice guidelines promulgated by the American Heart Association emphasize immediate recognition of cardiac arrest with the institution of effective chest compressions and early electrical shock therapy for ventricular fibrillation.[40] The guidelines emphasize the delivery of uninterrupted chest compressions, with the caregiver's hands placed over the lower half of the sternum. Compression excursion should be at least two inches at a rate of at least 100 compressions per minute to ensure that compressions are of sufficient depth, that the chest wall returns to its normal position between compressions, and that compres-

sions are not interrupted. Complete recoil of the sternum prior to the following compression is recommended. The guidelines specifically recommended that chest compressions not be interrupted for advanced airway interventions or to obtain vascular access for administration of drugs. It is useful for practicing surgeons to maintain current training status in Advanced Cardiovascular Life Support. Reviewing the complete guidelines document is also suggested; these guidelines are available for free on the American Heart Association website at *www.heart.org*.

Data cited by Ramsay and Maxwell[37] indicated that chest compressions without rescue breaths result in improved outcomes for cardiopulmonary resuscitation in witnessed out-of-hospital cardiac arrest events. A more favorable neurologic outcome, more frequent occurrence of shockable cardiac rhythm on initial electrocardiogram, and improved overall survival were all confirmed in the study when resuscitation began within four minutes of cardiac arrest. These observations have lent support to the primacy of supplying effective chest compressions.

Data confirming the effectiveness of "compression-only" CPR were presented in an article by Dumas and coauthors[41] in *Circulation,* 2013. The article is supplied as a full-text reprint accompanying some formats of *SRGS*. The authors performed a retrospective cohort study using data gathered for two randomized controlled trials. They were able to compare long-term outcomes of more than 1,200 patients resuscitated with chest compressions plus rescue breathing with a similar-size group of patients resuscitated with chest compressions alone. Long-term survival was improved in patients who received chest compressions alone. Additional data reported in an article by Hasegawa and coauthors[42] in *JAMA,* 2013, provided confirmation of the findings reported by Dumas and associates. Hasegawa and colleagues reported outcomes data on more than 640,000 Japanese patients who sustained out-of-hospital cardiac arrest and were resuscitated by emergency personnel. The analysis showed that patients who were resuscitated with CPR plus advanced airway management had worse outcomes compared with patients who had resuscitation with chest compressions alone. Available data support the advantage of chest compressions that are applied with a frequency of at least 100 compressions per minute with adequate excursion compared with older approaches.

Despite dissemination of this information nationally, there is evidence from data cited by Ramsay and Maxwell[37] that there is an unsatisfactory level of compliance with these guidelines. In a study of in-hospital cardiac arrest cited by the authors, a compression rate of less than 100 per minute was observed in more than 90% of resuscitations. An additional finding of this study was a disturbing frequency of "no-flow" intervals (intervals during which there are no compressions). These exceeded 10 seconds per minute of resuscitation events.

An additional cause of interruption of compressions in patients who develop cardiac arrest is endotracheal intubation. An article by Andersen and coauthors[43] in *JAMA,* 2017, reported data from a large national database comparing patients who had endotracheal intubation performed during the first 15 minutes of cardiopulmonary resuscitation with propensity score-matched patients who did not have endotracheal intubation during similar intervals. The data analysis showed that endotracheal intubation was associated with a significantly poorer survival to hospital discharge. In the discussion section of their report, the authors explained that previous studies associated endotracheal intubation with decreased survival to hospital discharge; that said, at least one large meta-analysis showed no association of intubation with decreased survival. The authors hypothesized that intubation might be associated with intervals of interrupted cardiac compressions, hyperoxia, esophageal intubation, delay of administration of needed drugs such as epinephrine, and episodes of hypoxemia. They concluded that endotracheal intubation should be undertaken with caution in patients undergoing cardiopulmonary resuscitation.

In an editorial that accompanied the article, Angus[44] commented that although there has been a shift from an emphasis on early airway control during cardiopulmonary resuscitation (airway-circulation-breathing) to an emphasis on beginning and sustaining adequate cardiac compressions (circulation-airway-breathing), current recommendations still consider airway management an important component of in-hospital cardiopulmonary resuscitation. The data presented in the article by Andersen and coauthors[43] do not categorically prove that

endotracheal intubation is harmful, but the lesson that can be drawn from this analysis is that resuscitation teams should develop protocols for airway management that will result in adequate oxygenation while preserving cardiac compressions.

The updated guidelines[40] have continued support for epinephrine injection as an adjunct to cardiopulmonary resuscitation. Readers are encouraged to review the guidelines document for updated information on the use of epinephrine and other pharmacologic agents.

Pearson and coauthors[45] focused on the potential for outcomes of cardiopulmonary resuscitation to be improved through formal protocolized quality improvement interventions in *Resuscitation,* 2016. The authors analyzed outcomes after the institution of a team-focused training effort across an entire state. The outcomes were recorded for all out-of-hospital cardiac arrest events. The analysis showed that there was significant improvement in good neurologic outcomes after the quality improvement initiative was completed. The authors concluded that this training was beneficial for emergency medical personnel and their patients and that these findings suggest that improved outcomes from the use of team training for in-hospital cardiac arrest might be realized as well.

The use of mild hypothermia had been recommended in practice guidelines for cardiac arrest patients who do not show immediate neurologic recovery. This topic was the focus of a retrospective medical record review reported by Wang and coauthors[46] in the *American Journal of Emergency Medicine,* 2013. The authors compared 51 patients who had early mild hypothermia added to conventional supportive care after CPR with 124 patients who had standard supportive care without hypothermia. The main outcome analyzed was survival to hospital discharge and neurologic status at hospital discharge. The analysis showed that survival was improved with the use of hypothermia (14 of 51 patients vs. 12 of 124 patients). A good neurologic outcome was recorded in 7.9% of hypothermia patients compared to 1.7% of patients who had standard care. The authors concluded that mild therapeutic hypothermia is potentially helpful for patients who survive CPR but have delayed return of neurologic function. Additional data[47] have documented the safety of mild hypothermia. Of note is that mild hypothermia is recommended in the practice guidelines of the Advanced Cardiovascular Life Support course sponsored by the American Heart Association.

Another approach to applying hypothermia and circulatory support for victims of cardiac arrest is with the use of extracorporeal membrane oxygenation. This topic was discussed in a report by Thiagarajan and coauthors[48] in *Annals of Thoracic Surgery,* 2009. This article is a report of an analysis of a large extracorporeal membrane oxygenation database. Eleven percent of patients in the database had the device applied as an adjunct to management of cardiac arrest. The most frequent diagnosis recorded was "cardiac disease." The authors documented a 27% survival rate in these patients. The proportion of in-hospital vs. out-of-hospital cardiac arrests was not provided and the presence of a shockable rhythm is likewise unknown. These data suggested the potential utility of the extracorporeal membrane oxygenator in patients sustaining cardiac arrest. Improved outcomes occurred when the device was applied within two hours of arrest. A diagnosis other than myocarditis was also associated with improved survival. Renal insufficiency requiring dialysis was associated with increased mortality risk. Additional discussion of extracorporeal membrane oxygenator support will be presented in a later section of this review that covers the management of adult respiratory distress syndrome (ARDS).

Editorial Comment

The features of successful resuscitation of patients who sustain out-of-hospital or in-hospital cardiac arrest are important components of the knowledge base of surgeons. Resuscitation maneuvers such as chest compressions and ventilation maneuvers are frequently not performed in compliance with recommendations from national bodies such as the American Heart Association. It is important to recall that maneuvers to provide effective chest compression and optimum venous return to the heart are critical features leading to successful resuscitation. Surgeons will be consulted to assist in the management of injuries sustained during cardiopulmonary resuscitation. Injuries from cardiopulmonary resuscitation are relatively common, with clinically significant injuries discovered

in 10%–15% of autopsied patients. Injuries may be discovered in a larger proportion of survivors. Rib fracture and/or costochondral separation are the most commonly diagnosed injuries. Pneumothorax, hemothorax, diaphragm injury, and lacerations of the liver and spleen are occasionally encountered as well.

Perioperative Respiratory Complications

Respiratory complications after major surgical procedures might range from minor problems (e.g., microatelectasis that can be cleared with coughing, deep breathing, and early ambulation) to major, life-threatening events such as postoperative respiratory failure. Risk of major respiratory failure requiring ventilatory intervention is increasing as the surgical patient population ages and the frequency of preexisting respiratory diseases (e.g., chronic obstructive pulmonary disease [COPD] and obstructive sleep apnea) increases. The proinflammatory state stimulated by anesthesia, operation, and transfusion can produce lung injuries that may progress to acute respiratory distress syndrome. In order to minimize the negative impact of postoperative respiratory complications, surgeons require knowledge of the pathophysiology of these complications, effective preventive measures, features of diagnosis, and effective treatment approaches.

Sachdev and Napolitano[49] reviewed perioperative respiratory complications in *Surgical Clinics of North America,* 2012. The authors noted that postoperative pulmonary complications are most common after thoracotomy (20%–60%), depending on the definition of a complication. By contrast, pulmonary complications occur in 20% or less of patients undergoing abdominal operations.

Risk Factors for Respiratory Complications

Sachdev and Napolitano stated that patient-related characteristics are important predictors of postoperative pulmonary complications. Risk factors for the development of pulmonary complications after abdominal operations include older age, ASA score of 2 or higher, COPD, congestive heart failure, and dependent functional status. Evidence cited by the authors supports the conclusion that current smoking and poorly controlled asthma are also risk factors for postoperative pulmonary complications after abdominal procedures. Other factors that impact the risk of postoperative pulmonary complications are alcohol use, impaired sensorium, and preoperative weight loss. Obstructive sleep apnea was also identified as a risk factor for postoperative pulmonary complications. The authors suggested that patients undergoing procedures known to be associated with postoperative pulmonary complications (thoracotomy, gastrointestinal procedures, and abdominal vascular procedures) are good candidates for risk assessment and efforts to minimize risk of complications by using preoperative and postoperative interventions.

Additional information relevant to the risk of postoperative pulmonary complications in patients with obstructive sleep apnea was presented in a report by Kaw and coauthors[50] in the *British Journal of Anesthesia,* 2012. The authors stated that clinically significant obstructive sleep apnea is present in more than 11% of American men and more than 4% of women. Obesity and metabolic syndrome are important conditions associated with obstructive sleep apnea. As increasing numbers of patients with these comorbidities present for surgical treatment, plans for detection and management of obstructive sleep apnea will become important in the preoperative preparation of these patients.

The authors conducted a meta-analysis using standard techniques to evaluate the strength of evidence and the quality of the research studies included in the analysis. Thirteen studies that reported data on nearly 4,000 patients were included in the final analysis. The data showed that there were clinically important increases in the risks for postoperative respiratory failure and postoperative cardiac events in patients with obstructive sleep apnea who underwent operations. Risk increased more than

twofold for these two complications compared to the risk in patients without a diagnosis of obstructive sleep apnea. Although the data was limited by the heterogeneity of some of the studies included in the meta-analysis, there were also increases in risks for desaturation and transfer to an ICU postoperatively for patients with obstructive sleep apnea.

A task force organized by the American Society of Anesthesiologists developed practice guidelines for the perioperative diagnosis and management of patients at risk for obstructive sleep apnea in 2006 and these guidelines were updated in 2013.[51] The guidelines recommend that patients thought to be at risk for obstructive sleep apnea (according to findings in the history and physical examination) be evaluated using standard testing. The guidelines encourage open communication between surgeons and anesthesiologists so that decisions regarding preoperative interventions, such as training in continuous positive airway pressure (CPAP) devices, can be offered to help reduce the risk of postoperative complications. The guidelines recommend using local and regional anesthesia where feasible. Monitoring of breathing and oxygen saturation is recommended for patients receiving intraoperative sedation. Consideration of overnight admission may be appropriate in patients with obstructive sleep apnea. The guidelines document is available for free on the American Society of Anesthesiologists website at *www.asahq.org*.

As mentioned in the previous discussion, obstructive sleep apnea is being diagnosed with increasing frequency. The presence of this disorder in obese patients and patients with metabolic syndrome (obesity, hypertension, and hyperglycemia) is firmly established. Also mentioned previously, obstructive sleep apnea is predictive of postoperative respiratory complications. In *Anesthesiology*, 2009, Gali and coauthors[52] investigated the possibility that preoperative testing for obstructive sleep apnea might identify patients at an increased risk for episodes of postoperative hypoxemia. The authors opened their report by citing data indicating a substantial rate of underdiagnosis of obstructive sleep apnea. They referred to a 1993 report that estimated that 4% of men and 2% of women in the 30–60 year age group had obstructive sleep apnea and that this condition was an independent risk factor for postoperative mortality. By the end of the 1990s, there had been a twelvefold increase in the diagnosis of obstructive sleep apnea. Later estimates have concluded 82% of men and 93% of women with obstructive sleep apnea remain undiagnosed. It is likely that many of these individuals will require surgical care and that this group will be at an increased risk for perioperative respiratory complications. Gali and coauthors described the pathophysiology of respiratory complications in patients with obstructive sleep apnea. The anatomic and physiologic abnormalities of obstructive sleep apnea can be brought on by the diminished responses to hypoxia and hypercapnia as well as the diminished pharyngeal tone produced by anesthetic and analgesic medications. In the report, the authors hypothesized that a preoperative risk assessment for obstructive sleep apnea applied in patients not known to have obstructive sleep apnea coupled with postanesthesia monitoring for hypoxemic events will identify patients at risk and prevent complications. The preoperative assessment consisted of obtaining a sleep apnea clinical score. This score assigned points based on responses to questions about the presence of hypertension and a history of being told by persons sharing their sleeping area that they snore; for this latter question, one point was assigned for snoring 3–5 times/week or for snoring every night. The patients were also asked whether they have been told that they gasp, choke, or snort while sleeping. The point assignment for positive responses was based on the frequency of symptoms. The final assessment was a measurement of neck circumference. Points were assigned for various neck circumferences with hypertension, historic features, or both. A score of >15 indicated a high likelihood of obstructive sleep apnea.

Postoperative monitoring of the patients enrolled in this study included continuous oxygen saturation monitoring, and monitoring for apnea, bradypnea, and pain level/sedation mismatch. The last assessment was accomplished when a patient indicated severe pain on a visual-analog scale but appeared too sedated to receive additional analgesia. In all, 673 patients were enrolled. Sleep apnea scores of >15 predicted episodes of desaturation as well as recurrent potential hypoxemic events in the postanesthesia care area. The combination of a high sleep apnea score and postanesthesia area hypoxemic events predicted postoperative respiratory complications. A high sleep apnea clinical score was recorded in nearly 32% of this patient group; these patients had higher ASA scores as well. Patients with

high clinical scores and recurrent hypoxemic events in the postanesthesia care area had a frequency of diagnosed postoperative respiratory complications of 33%. Patients with low scores and recurrent postanesthesia events had a frequency of postoperative respiratory complications of 11%. Patients with low scores and no events developed postoperative respiratory complications in less than 1% of patients.

The authors noted that the gold standard for diagnosis of obstructive sleep apnea is polysomnography. Validation of the sleep apnea clinical score with comparison to other scores and polysomnography are found in two older articles.[53, 54] These studies, conducted in 1994 and 2003, confirmed that the sleep apnea clinical score has a positive predictive value for an accurate diagnosis of obstructive sleep apnea of more than 80% when compared to polysomnography. A limitation of the study by Gali and associates[52] is that polysomnography was not used to validate the findings reported. Nonetheless, the data suggest that obstructive sleep apnea may be underdiagnosed. Furthermore, sleep apnea clinical scores >15 were, when combined with assessments performed in the postanesthesia care area, predictive of postoperative respiratory complications. Finally, this straightforward assessment can be used to identify patients at risk.

Editorial Comment

Easily obtained information from the history and physical examination could identify patients for polysomnography and/or preventive interventions, such as continuous positive airway pressure. Information on a history of hypertension, snoring, obesity, and neck circumference >17 inches would provide a basis for further evaluation.

Prevention of Respiratory Complications

Sachdev and Napolitano[49] presented a table containing interventions used to prevent postoperative pulmonary complications that are and are not supported by available evidence (Figure 5). The authors stressed that interventions such as smoking cessation need to begin preoperatively.

Figure 5

Specific interventions for prevention of postoperative pulmonary complications with assessment of the strength of supporting evidence. Note: A= Strong evidence; B= Moderately strong evidence; C= Weak evidence; I= Indeterminate evidence; D= Significant evidence that potential for harm outweighs potential benefit. Reproduced from Sachdev and Napolitano[49] with permission.

Specific interventions to reduce the risk for postoperative pulmonary complications

Risk-Reduction Strategy	Strength of Evidence[a]	Type of Complication Studied
Postoperative lung expansion modalities	A	Atelectasis, pneumonia, bronchitis, severe hypoxemia
Selective postoperative nasogastric decompression	B	Atelectasis, pneumonia, aspiration
Short-acting neuromuscular blockade	B	Atelectasis, pneumonia
Laparoscopic (vs open) operation	C	Spirometry, atelectasis, pneumonia, overall respiratory complications
Smoking cessation	I	Postoperative ventilator support
Intraoperative neuraxial blockade	I	Pneumonia, postoperative hypoxia, respiratory failure
Postoperative epidural analgesia	I	Atelectasis, pneumonia, respiratory failure
Immunonutrition	I	Overall infectious complications, pneumonia, respiratory failure
Routine total parenteral or enteral nutrition[b]	D	Atelectasis, pneumonia, empyema, respiratory failure
Right-heart catheterization	D	Pneumonia

Hawn and coauthors[55] analyzed the impact of smoking on the risk of postoperative complications in *Annals of Surgery,* 2011. The authors obtained data from a national Veterans Affairs Health System database. Data from nearly 400,000 patients who underwent a surgical procedure over a six-year interval were analyzed. Patients were categorized into groups of current smokers, prior smokers, and never-smokers. The analysis showed that current smokers had a significantly increased risk of postoperative pneumonia, surgical site infections, and mortality. The risk rose incrementally for each 10 pack-years of smoking. Hawn and colleagues cited evidence of the production of tissue hypoxia that increases the risk of surgical wound infections. Adverse effects on fibroblasts from toxins in cigarette smoke impair cell migration and the wound healing response. Additional evidence cited

by the authors supported the conclusion that smoking produces long-term pulmonary damage even without clinical evidence of COPD. Animal data cited in the article suggested that exposure to cigarette smoke reduces the ability of the lung to resist infection. The authors concluded that their data support the use of preoperative smoking cessation interventions.

Musallam and coauthors[56] presented additional information on the impact of smoking on the risk of postoperative complications in *JAMA Surgery,* 2013. The authors queried the ACS NSQIP database and analyzed data from more than 600,000 patients. The analysis confirmed a significant increase in mortality risk, pulmonary complications, and vascular complications in current smokers. Of note was that the NSQIP data allowed for the identification of patients who had not smoked for at least a year. The increased risk of complications was eradicated in this group. The authors concluded that efforts at smoking cessation are potentially important in reducing surgical complications.

The optimum interval for preoperative smoking cessation prior to operation is controversial. Sachdev and Napolitano[49] cited data from a study of patients undergoing coronary artery bypass that suggest an increased risk of postoperative pulmonary complications for patients who stop smoking less than eight weeks prior to operation. By contrast, a meta-analysis by Mills and coauthors[57] in the *American Journal of Medicine,* 2011, evaluated data from six randomized trials and 15 observational studies. They found evidence supporting a benefit of smoking cessation at least four weeks prior to operation and reported no evidence of harm for smoking cessation intervals of at least four weeks. The beneficial effect of smoking cessation increased incrementally for each week of smoking cessation beyond four weeks. When data from all of the randomized studies were pooled, there was a 41% reduction of postoperative pulmonary complications after smoking cessation. For each week beyond four weeks of cessation, there was a 19% risk reduction from smoking cessation. Mills and colleagues estimated that effective smoking cessation interventions could potentially prevent 2 million postoperative complications. The available data support the use of smoking cessation interventions to achieve an interval of nonsmoking of at least four weeks prior to an operation. Longer intervals of smoking cessation pay significant dividends in terms of reducing mortality and complication risks.

As discussed earlier, risk studies have identified systemic risk factors such as elevated ASA score, smoking, obesity, older age, and need for complex operation as significant predictors of postoperative respiratory complications. Congestive heart failure and COPD are patient-specific factors that are potentially modifiable. It is well-recognized that smoking cessation and measures to stabilize cardiovascular disease may require two months or more of preoperative effort in order to meaningfully impact complication risks. Lung-specific interventions (e.g., treatment of lung infection, sputum-reduction measures, use of bronchodilators, and preoperative respiratory muscle training) also have potential value.

Preoperative Maneuvers

Sachdev and Napolitano[49] indicated that additional preoperative maneuvers to lower the risk of postoperative pulmonary complications usually focus on optimizing the status of any preexisting lung disease. For example, patients with known COPD may benefit from antibiotic therapy to eradicate infection, bronchodilator therapy, and systemic glucocorticoid therapy in selected patients. The authors observed that data regarding the use of systemic glucocorticoid therapy in patients with asthma has been inconclusive, but consideration of this intervention may be useful in selected patients with poorly controlled asthma. For these conditions, therapeutic approaches will need to be individualized based on risk assessment for each patient.

An article focusing on the preoperative pulmonary evaluation of elderly patients was by Gore[58] in *Gerontology,* 2007. The author opened their review by emphasizing the clinical importance of abnormal postoperative ventilation, hypoxemia, and hypercarbia; these lead to the need for intubation and mechanical ventilator support. Dysfunctional ventilation leading to intubation greatly increases the risk of ventilator-associated pneumonia (VAP) that is associated with a mortality risk exceeding 50%. Mortality rates for VAP have not changed over many years.

This consistent observation supports the importance of preventive strategies to reduce the need for intubation in this patient group.

Particular problems that may predispose elderly patients to perioperative respiratory complications include a gradual decline in one-second forced expiratory volume (FEV1) with advancing age and increased ventilation/perfusion mismatching, which is caused by increased early airway closure in dependent lung units. Gore cited data that documented decreased FEV1 as an accurate predictor of postoperative respiratory complications. Ventilation/perfusion mismatching causes an age-related decline in resting arterial oxygen tension. Furthermore, older patients develop blunted responses to hypoxemia and hypercarbia and are vulnerable to analgesic and sedative-induced respiratory depression. Age-related decreases in mucociliary function reduce clearance of bacteria from the airway and contribute to increases in perioperative pneumonia risk. This abnormality is particularly pronounced in smokers. Gore suggested careful history-taking to detect reactive airway disease, allergy, cough, and excessive sputum production. The degree of chronic cough can be ascertained using a "cough test." The patient is asked to cough: if the cough results in production of sputum or repeated coughing, additional testing (such as quantification of FEV1) may be helpful. If excessive sputum production is documented, a sputum culture is recommended. Recovery of a pathogen such as *H. influenzae, S. pneumoniae*, or MRSA can prompt a short course of preemptive antibiotics. Additional interventions that can strengthen cough and reduce sputum production include postural drainage, assisted cough, and deep-breathing exercises.

Inhaled bronchodilators are indicated preoperatively in patients with reactive airway disease and in patients with chronic bronchitis. Data cited by Gore suggest that ipratropium bromide (Atrovent®) is a useful first-line inhalant. Aminophylline has also been used for this purpose, but data cited by Gore suggest that the association of this drug with tachycardia limits its use for elderly surgical patients. In patients with documented COPD, preoperative corticosteroid therapy may be useful. The effectiveness of steroid therapy is monitored with sequential assessments of FEV1. If this variable improves with steroid therapy, preoperative and postoperative therapy is valuable. Gore stressed data suggesting that less than one-third of COPD patients will have significant responses to corticosteroids, although degrees of improvement in some patients are substantial. Gore emphasized the importance of continuing preoperative therapy into the postoperative recovery period.

Intraoperative Interventions

Sachdev and Napolitano[49] stated that the anesthetic technique used for an operative procedure might influence the risk for postoperative pulmonary complications. They cited data indicating that the use of long-acting neuromuscular blocking drugs such as pancuronium is associated with an increased risk for postoperative pneumonia (13% compared with 5% for shorter acting agents). Additional data is cited from a prospective study that showed a fourfold increase in the risk of postoperative pneumonia with the use of long-acting neuromuscular blocking agents. Additional risk reduction might be achieved by using regional anesthesia or epidural analgesia combined with inhalational agents. An article by Levy and coauthors[59] reported data from a cohort study of patients with known COPD. Patients with known COPD, 541 in total, underwent major abdominal surgery in a single center over a 12-year interval. The propensity score method was used to achieve patient matching. Endpoints considered were postoperative pneumonia and overall mortality. Patients who had epidural analgesia combined with inhalational anesthesia had reduced risks of both pneumonia and mortality. With multivariate analysis, the risk reduction for postoperative pneumonia was statistically significant.

Postoperative Maneuvers

Time-honored patient care processes for minimizing postoperative pulmonary complications include early ambulation, encouraging cough, elevation of the head of the bed, and judicious use of systemic analgesics and sedation. These interventions are valuable for preventing atelectasis and maintaining lung inflation. Sachdev and Napolitano[49] cited data supporting several interventions that might facilitate efforts to prevent postoperative atelectasis and pneumonia in patients undergoing abdominal operations. One such intervention is selective use of

nasogastric intubation. The presence of the nasogastric tube causes pharyngeal irritation and swelling and might raise the risk of microaspiration.

Data from several studies suggest an increase in the risk of postoperative pulmonary complications with postoperative nasogastric intubation. Nasogastric intubation can be safely omitted in patients at low risk for gastric distention and in patients who do not have an upper gastrointestinal anastomosis. In patients who are alert postoperatively, with low nasogastric drainage volumes, early removal of the nasogastric tube can be considered. The authors also cited data indicating reduction of postoperative pneumonia risk in patients treated with patient-controlled analgesia and combinations of patient-controlled and epidural analgesia. There is a general consensus that early ambulation is helpful for improving lung inflation and lowering the risk of postoperative pulmonary complications. Sachdev and Napolitano commented on other interventions, indicating that data are inconclusive regarding the benefit of incentive spirometry. Available data does not support the use of CPAP or intermittent positive pressure breathing.

A randomized trial evaluating intensive inspiratory muscle training under the supervision of a physical therapist as a means of reducing perioperative respiratory complications was by Dronkers and coauthors[60] in *Clinical Rehabilitation*, 2008. In this study, 20 patients undergoing open abdominal aortic aneurysm repair were randomized to receive intensive inspiratory muscle training (one physical therapist-supervised session and five unsupervised sessions per week for two weeks prior to operation). This group was compared to a control group that received instruction in deep breathing and incentive spirometer use. The primary endpoint of this study was detection of atelectasis on chest radiograph. The analysis disclosed a nonsignificant trend toward less atelectasis in the group that received intensive inspiratory muscle training. Maximum inspiratory force increased by 10% in the intervention group. Patient satisfaction with the intervention was high. The authors acknowledged the need for additional studies involving larger patient groups.

A meta-analysis of available data from studies evaluating prophylactic respiratory physical therapy was by Pasquina and coauthors[61] in *Chest*, 2006. The authors evaluated 35 trials that provided data on the possible value of respiratory physical therapy in preventing perioperative respiratory complications. The authors found that significant differences in postoperative respiratory events were reported in only four studies that included a "no intervention" control group. In the studies, differences occurred in the frequency of atelectasis (usually defined as a change on chest radiograph). Most studies did not focus on important complications such as pneumonia, need for intubation, or ventilator support. In the single study that analyzed the effects of respiratory physical therapy on the frequency of pneumonia, a significant reduction was recorded, but the frequency of pneumonia in the control group was higher than baseline rates for this complication recorded in other clinical series. This fact limits the external validity of this study. Unspecified respiratory complications were reduced in one analysis. The authors concluded that routine use of physiotherapy is not indicated in low- and moderate-risk patients undergoing abdominal operations. There were no reports of adverse events associated with the use of physical therapy.

Experience from ICUs has led to increasing use of "bundled" care processes for prevention of complications. Guidelines for pneumonia prevention are available for critical care units, but these approaches have not been used often for pneumonia prevention in postoperative patients who are not in an ICU. Wren and coauthors[62] presented a report on introducing and using a care process bundle to reduce postoperative pneumonia risk in nonintensive care settings; their article was published in the *Journal of the American College of Surgeons,* 2010, and is supplied as a full-text reprint accompanying some formats of *SRGS*.

The authors conducted a "before and after" study in a single hospital. Baseline rates of postoperative pneumonia were determined based on hospital-specific data from the ACS NSQIP database. A list of evidence-based interventions was compiled including early ambulation, deep-breathing exercises with incentive spirometry, elevation of the head of the bed, protocol-based pain control, and twice daily chlorhexidine oral hygiene. Medical and nursing staff training was conducted and a pneumonia prevention order set was integrated into the electronic medical record system of the hospital. Documentation of the prevention bundle was included in nursing records.

The analysis showed that the baseline rate of postoperative pneumonia was 0.78%. In the "after" cohort of patients, the pneumonia rate decreased to 0.18%, a reduction of 81%. The authors stressed the importance of ongoing education, optimum team function, and periodic feedback as means of promoting adoption and consistent use of the care bundle and concluded that a simple group of evidence-based interventions, applied consistently, can significantly reduce postoperative pneumonia risk.

Editorial Comment

In this section, we have discussed preoperative, intraoperative, and postoperative maneuvers that are potentially useful for preventing postoperative pulmonary complications. Interpreting the available data is challenging because of the variable definitions of respiratory complications and the small patient groups that make up most of the available studies. Available evidence supports the conclusion that most patients undergoing abdominal or thoracic operations should have early ambulation, selective use of nasogastric intubation, elevation of the head of the bed, training in coughing and deep breathing, and careful pain control. Interventions such as preoperative antibiotics, inhaled bronchodilators, continuous positive airway pressure breathing, and corticosteroids may be used in carefully selected patients.

Acute Respiratory Distress Syndrome

ARDS was first described by Ashbaugh and coauthors[63] and is a term applied to a complex response pattern of pulmonary cell populations to systemic and localized inflammatory stimuli. A multitude of injuring agents, acting singly or in combination, can produce the histologic, radiologic, and clinical manifestations of ARDS. These agents might act by direct injury to the lung tissue (pulmonary contusion, pulmonary blast injury) or to the airway (aspiration, inhalation injury). In other instances, the inflammatory process begins with a remote stimulus (peritonitis, pancreatitis, sepsis, combined traumatic injury, shock, and resuscitation) and the lung is injured because of circulating factors that act directly on the lung microcirculation and/or lung tissue or through activation of inflammatory mediators within the lung microcirculation. Pneumonia can trigger injuries in the adjacent noninfected lung through propagation of the inflammatory process.

Patients may recover from mild ARDS or progress to severe ARDS, a clinical entity that is manifest by hypoxemia due to ventilation/perfusion mismatching, loss of lung compliance due to alveolar flooding and consolidation of lung tissue, and increased dead space ventilation resulting from pulmonary microvascular occlusion. Support of ventilation and oxygenation using adjuvant ventilation therapies can assist the lungs in the effort to maintain oxygen transfer from alveolus to blood, but these therapies have no positive effect on the severity or clinical course of acute respiratory distress syndrome. In fact, as clinicians have learned over the past decade, adjuvant ventilator therapy can additionally injure the lungs through the effects of pressure, volume, cycling of ventilation, and promotion of the inflammatory process.

An international consensus definition of ARDS was presented in a 2012 article in *JAMA*.[64] The article presented the results of an expert panel review process sponsored by the European Society of Intensive Care Medicine and endorsed by the American Thoracic Society and the Society of Critical Care Medicine. The final definition (Berlin definition) proposed three mutually exclusive categories of ARDS based on severity of hypoxemia as expressed by the ratio of arterial oxygen partial pressure to the fraction of inspired oxygen (PaO_2/FIO_2). Mild ARDS was defined as PaO_2/FIO_2>300 mm Hg, moderate ARDS as PaO_2/FIO_2<200 mm Hg, and severe ARDS as PaO_2/FIO_2<100 mm Hg. An additional four ancillary variables were proposed for severe ARDS including radiographic severity, compliance <40 mL/cm H_2O, required positive end-expiratory pressure (PEEP) of >10 cm H_2O, and corrected expired volume <40 mL/cm H_2O. The report provided a validity analysis using seven patient data sets that included nearly 4,500 patients. The analysis showed

that there was moderately good predictability of mortality and the need for intensive ventilator support based on the severity grades, but there was no contribution of the ancillary measures to the predictive value. The consensus report specifically defined the term "acute" as meaning that clinical symptoms were present for one week or less. The consensus definition committee also recommended eliminating the term "acute lung injury." The authors concluded that the severity grading system would be useful in guiding therapeutic choices and subdividing patients for purposes of research. Figure 6 summarizes the Berlin definition.

In an editorial that accompanied the consensus definition article, Angus[65] praised the effort to provide a needed severity definition. In addition, he pointed out the need for an expansion of the clinical definition to include patients who may not have severe enough disease to require ventilator support. Angus also suggested that the analysis be expanded in the future to consider long-term outcomes.

Pathophysiology of ARDS

Figure 6 The Berlin definition of acute respiratory distress syndrome. Reproduced from Force and coauthors[64] with permission.

The Berlin Definition of Acute Respiratory Distress Syndrome

	Acute Respiratory Distress Syndrome
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild	200 mm Hg $<$ $Pa_{O_2}/F_{IO_2} \leq$ 300 mm Hg with PEEP or CPAP $\geq$5 cm H_2O[c]
Moderate	100 mm Hg $<$ $Pa_{O_2}/F_{IO_2} \leq$ 200 mm Hg with PEEP $\geq$5 cm H_2O
Severe	$Pa_{O_2}/F_{IO_2} \leq$ 100 mm Hg with PEEP $\geq$5 cm H_2O

Abbreviations: CPAP, continuous positive airway pressure; F_{IO_2}, fraction of inspired oxygen; Pa_{O_2}, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.
[a] Chest radiograph or computed tomography scan.
[b] If altitude is higher than 1000 m, the correction factor should be calculated as follows: [Pa_{O_2}/F_{IO_2} × (barometric pressure/760)].
[c] This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

Biomarkers of inflammation, altered coagulation, fibrinolysis, and increased oxidative stress are activated, elevated, or suppressed to varying degrees and with different trajectories in all of the inflammation-mediated diseases, including ARDS. Proinflammatory cytokines can be recovered from blood and from alveolar fluid in animals and patients with ARDS. Elevations of some biomarkers such as interleukin-6 (IL-6), interleukin-8 (IL-8), and intercellular adhesion molecule-1 (ICAM-1) are associated with worse clinical outcomes for ARDS. This is also true for coagulation factors. Lower levels of protein C and elevations of thrombomodulin indicate a procoagulant state; this pattern is associated with worse outcomes. Finally, impaired fibrinolysis is indicated by elevations of plasminogen activator inhibitor-1 (PAI-1) and elevated levels of this substance have been associated with worse outcomes of ARDS. The complex pathophysiology of lung damage is produced by inflammatory injury to the lung microcirculation, the alveolar capillary interface, and the airways. Each component is present, to varying degrees, depending on the agent producing the inflammatory state and the resulting lung injury. Recent research has further clarified the roles of the various mediator systems in the development and progression of ARDS.

Matthay and Zemans[66] provided a useful review article that examined various aspects of the epidemiology and pathophysiology of ARDS in *Annual Reviews of Pathology and Mechanisms of Disease,* 2011. The authors confirmed that ARDS is diagnosed in approximately 200,000 critically ill patients annually in the United States and carries a 40% mortality risk. Resolution of the disease is often prolonged because damage to the alveolar capillary membrane prevents removal of edema fluid and depresses the production of surfactant. The initiating pathophysiologic event in ARDS is damage to the pulmonary microcirculation with a resulting increase in permeability leading to the accumulation of edema fluid in the interstitium of the lung and in the alveolar spaces. This process is mediated by neutrophils, chemokines, and cell-surface molecules that act directly on the lung endothelium. The authors concluded by noting that therapeutic approaches such as ventilator support and extracorporeal oxygen-

ation have been the mainstays of treatment for ARDS for decades. Encouraging animal research suggests that stem cell therapies may be potentially useful in treating ARDS as well.

Eltzschig and coauthors[67] examined the role of purinergic signaling in the evolution of ARDS in the *New England Journal of Medicine,* 2012. The authors explained that components of the purinergic signaling system (ATP, ADP, and adenosine) are among the oldest biochemical molecules known to science. These molecules exert physiologic activity by binding with cell surface receptors that are G-protein coupled or ligand-gated ion channels. The net effect of interactions of these molecules with the cell surface ion channels is determined by the ratio of ATP and ADP to adenosine. Inflammation can cause the release of ATP and ADP from cellular stores in leucocytes and platelets. These molecules might be released in large quantities by cellular necrosis or in a more regulated fashion by apoptosis of leucocytes and platelets. The interaction of released ATP and ADP with P2 receptors on endothelial cells, dendritic cells, and other cell populations can contribute to the progression of the inflammatory process. Mice that are genetically altered so that P2 receptors are absent are protected from damage that occurs from inflammation. In the extracellular space, ATP and ADP are converted to adenosine by a progressive enzymatic process. Adenosine is transported to the intracellular space of many cell types. The transport of adenosine into inflammatory cells tends to blunt the inflammatory process. ATP and ADP accelerate lung inflammation in animal models of ARDS, while receptors that enhance the transport of adenosine to the intracellular space reduce lung inflammation. The authors affirmed that acceleration of intracellular transport of adenosine has potential value as a therapeutic strategy in ARDS.

Calfee and coauthors[68] analyzed the relationship between inflammatory mediators and ARDS outcomes in humans in *Critical Care Medicine,* 2012. These investigators evaluated changes in angiopoietin-2 serum levels in patients with ARDS from infectious and noninfectious etiologies. The analysis showed that elevations of angiopoietin-2 were a marker for increased mortality risk in patients with noninfectious lung injuries. Angiopoietin-2 levels were increased in survivors and nonsurvivors of ARDS, but a progressive increase in angiopoietin-2 levels over the first three days after the onset of an infection-related lung injury was a consistent marker of increased mortality risk.

Progression of ARDS to scarring and fibrosis of lung tissue is associated with fibroblast migration into lung tissue. An article by Piednoir and coauthors[69] focused on the role of alveolar fluid in the progression of lung fibrosis in *Critical Care Medicine,* 2012. The authors pointed out that fibroblast migration into damaged lung tissue can promote healing of alveolar damage—but that it can also contribute to lung fibrosis that produces scarring in the later stages of ARDS. The study results showed that alveolar fluid promoted fibroblast migration through the actions of platelet-derived growth factor and a soluble platelet-derived growth factor metabolite. The balance between these two factors determined the amount of fibroblast migration that occurred. Promotion of fibroblast migration was associated with improved 28-day mortality rates in patients with ARDS.

Another study evaluating the potential value of therapies that modulate inflammatory mediators in lung alveolar fluid was by Wohlauer and coauthors[70] in *Critical Care Medicine,* 2012. The authors treated animals with shock-induced ARDS with inhaled nebulized hypertonic saline. Animals treated with the inhalant therapy had attenuation of lung injury that was associated with reduced levels of matrix-metalloproteinase-13. In an editorial accompanying the article, Kaplan[71] opined that additional long-term studies of this intervention could potentially lead to clinical trials. He cautioned, however, that delivery of hypertonic saline in the setting of intravenous fluid therapy with normal saline could produce hyperchloremic metabolic acidosis, which has been associated with an increased mortality risk in critically ill patients.

Transfusion-Related Lung Injury

Blood transfusion is one known cause of lung injury that can progress to ARDS. Vlaar and coauthors[72] reviewed clinical features of transfusion-related acute lung injury (TRALI) in cardiac surgery patients in *Critical Care Medicine,* 2012. The authors prospectively evaluated serum and alveolar fluid levels of proinflammatory mediators and inflammation-suppressing cytokines in

patients with TRALI after cardiac surgical procedures. From a total cohort of 668 patients, the investigators were able to match patients who developed TRALI with transfused and non-transfused patients who did not develop TRALI. Patients who developed TRALI were older and had longer intervals of cardiopulmonary bypass. Serum levels of proinflammatory mediators were increased in all patients. Increased production of lung fluid rich in proinflammatory mediators was consistently observed in patients with TRALI. Progression of TRALI was associated with depressed levels of the antiinflammatory cytokine plasminogen activator in alveolar fluid. In an accompanying editorial, Silliman[73] explained that patient age and duration of cardiopulmonary bypass may "set the stage" for a second insult to the lung delivered by mediators in transfused blood. He stressed that detection of these substances is difficult but that restrictive transfusion protocols should be evaluated in patients at an increased risk for TRALI.

Risk Factors for ARDS

Surgeons are most likely to encounter ARDS in patients with severe inflammatory processes resulting from infectious and noninfectious causes (pancreatitis, peritonitis) and in patients sustaining severe injury, especially from blunt mechanism. ARDS is diagnosed based on the findings of hypoxemia and pulmonary infiltrates observed on chest imaging.

Risk factors for developing ARDS in postoperative patients were analyzed in a study by Blum and coauthors[74] in *Anesthesiology,* 2013. The authors reviewed outcomes data from 50,367 patient admissions. All patients underwent general surgical operations (primarily gastrointestinal procedures). ARDS developed in 0.2% of patients. Preoperative factors associated with the development of ARDS included ASA score >2, older age, renal failure, COPD, and the need for an emergency operation. Intraoperative factors included the volume of electrolyte solution infused (liters), the need for blood transfusion, the need for high fraction of inspired oxygen, and the number of episodes of general anesthesia during the index admission. The authors concluded that ARDS is a rare but significant postoperative complication that clusters in older, more severely ill patients who require emergency operations.

Becher and coauthors[75] presented data on risk factors for ARDS development in injured patients in the *Journal of Trauma and Acute Care Surgery,* 2012. The authors observed that most instances of ARDS in trauma patients occurred in patients with blunt pulmonary injury (pulmonary contusion). They hypothesized that the percent of lung involved with pulmonary contusion calculated on admission imaging could predict the risk of ARDS. Their analysis showed that pulmonary contusion involving 24% or more of lung volume predicted the onset of ARDS with a sensitivity of 37% but a specificity of 94%. Positive and negative predictive values were 74%. The authors concluded that the percentage involvement of the lung with pulmonary contusion on admission imaging is potentially valuable as a means of predicting ARDS.

Another article that analyzed risk factors for ARDS in injured patients was by Watkins and coauthors[76] in *Critical Care Medicine,* 2012. The authors analyzed risk factors in a development cohort of 79 patients who developed ARDS. The patients were drawn from a total cohort of 223 participants in a randomized controlled trial. Factors found to be significantly associated with ARDS development were older age, higher injury severity, and illness severity (as judged by injury severity scores and APACHE II scores, blunt injury mechanism, presence of pulmonary contusion on admission imaging, flail chest, and massive transfusion). These criteria were applied in a validation cohort of more than 400 patients. The predictive model was moderately accurate, with an area under the ROC curve of 0.71.

Editorial Comment

The data provided by Watkins and coauthors document the correlation between age, increasing illness severity, infection, and acute respiratory distress syndrome. The role of inflammation in the genesis and as a driver of ARDS was confirmed in the clinical series. Younger patients with direct lung injury (trauma patients) are more likely, as a group, to survive. Ventilator strategies might also play a role in improved outcomes. The current approaches to ventilator support of patients with ARDS will be discussed in greater detail in the next section.

Clinical Strategies for Support of Oxygenation

This section will review contributions to the medical literature pertinent to ventilator therapy for patients with ARDS. We will also discuss the scientific basis and clinical effectiveness of "recruitment maneuvers" designed to reopen and maintain alveoli as well as evidence-based strategies for "weaning" the patient from ventilator therapy.

Patients admitted to the ICU are at risk for hypoxemia; recognition of this risk has led to supplemental oxygen being delivered by mask—even when clinical evidence of hypoxemia is not present—in an attempt to prevent unexpected hypoxemic episodes. Girardis and coauthors[77] compared empirical administration of supplemental oxygen (40% by mask) with a conservative supplemental oxygen support based on blood oxygen partial pressure targets. This report, which was published *JAMA,* 2016, described a prospective randomized trial comparing conventional oxygen therapy (mask oxygen with FIO_2 of 0.4 that was increased as needed to maintain PAO_2 at 100 mm Hg) to a conservative approach where oxygen was administered at the lowest concentrations possible to maintain PAO_2 at 70 mm Hg. The study enrolled more than 400 patients and the analysis showed that the conservative approach was associated with a significant reduction in intensive care mortality. Unfortunately, the study was closed long before the planned enrollment was achieved because of slow enrollment. These data suggest, but do not prove, that a conservative approach to oxygen administration in critically ill patients may be beneficial.

The approach to ventilator therapy for patients with ARDS has changed in one major and several minor ways over the past 3–5 years. Traditionally, the approach to ventilation has been designed to maintain oxygenation and ensure carbon dioxide removal. Importantly, surgeons are now aware of the potential patient harm that may accompany ventilator therapy. The effects of ventilator pressures and volumes on hemodynamics have been well recognized for many years. More recently, a group of phenomena has been associated with ventilator-induced lung injury; included in this category are:

Barotrauma (mediastinal emphysema, pneumothorax), which refers to lung damage due to disruption of alveoli resulting from excess alveolar pressures. Barotrauma can also result from the combination of rapid ventilator rates and positive end-expiratory pressure (PEEP), which produces "auto-PEEP," a phenomenon that produces successively increasing airway pressure because the rapid respiratory rate does not allow return of airway pressure to the set PEEP level before the next breath is delivered.

Volutrauma refers to alveolar damage caused by ventilation of compliant areas of the lung with large inspired volumes. The large volumes are delivered to compliant areas because consolidated areas of the lung lose compliance and the inspired gas is "shunted" to the compliant alveoli.

Atelectrauma is the term for alveolar injury that occurs from successive deflation and inflation of alveoli during the ventilator cycle. Unstable alveoli might collapse at end expiration and require reopening with the next inspiration, which produces injury to the alveolus. The "collapse-reopen" cycle also increases the intensity of the lung inflammatory response. Production of proinflammatory cytokines is stimulated and this phenomenon contributes to ventilator-associated lung injury.

The approach to minimizing ventilator-associated lung injury is based on an understanding that lung injury results from interactions of the ventilator cycle, mean airway pressure, and tidal volume. High mean airway pressure required to deliver high tidal volumes is the main cause of ventilator-associated lung injury. Approaches to lung-protective ventilation strategies emphasize the need to lower tidal volume and mean airway pressure. In patients with ARDS, microcirculatory obstruction and small airway obstruction may increase dead space ventilation to the extent that $PaCO_2$ rises. This rise can be made tolerable for the patient so that additional respiratory distress does not occur. The process of allowing $PaCO_2$ to increase is termed "permissive hypercapnia" and this is a component of lung-protective ventilation strategies. Data from randomized trials have demonstrated a significant reduction in mortality for acute respiratory distress syndrome with the use of lung-protective ventilation.

Meade and coauthors[78] presented a randomized prospective trial of a modified lung-protective ventilation protocol in *JAMA,* 2008. The authors compared a standard lung protective approach that used tidal volumes of 6 mL/kg, mean airway pressures of 30 cm H_2O or less, and a PEEP of 10 cm H_2O or less with an experimental approach that added an alveolar recruitment maneuver at the time of enrollment in the study and at each instance of airway disconnection. The recruitment maneuver included a sustained inspiration of 100% oxygen at an airway pressure of 40 cm H_2O for 1 minute. In addition, the experimental patient group had PEEP begun at 20 cm H_2O and reduced to produce optimum oxygenation. The experimental group was permitted to have airway pressures of 40 cm H_2O and patients were permitted to have "rescue" maneuvers (prone positioning, high frequency oscillating ventilation, and extracorporeal membrane oxygenation) when airway pressures could not be controlled and/or hypotension developed. When the results of the control and experimental groups were compared, all-cause mortality and the frequency of barotrauma (persistent pneumothorax after chest tube insertion or persistent pneumomediastinum) were not significantly different. Rates of refractory hypoxemia, death from refractory hypoxemia, and use of rescue therapies were all significantly lower in the experimental group.

Practice guidelines for managing sepsis and septic shock were published in 2013 and updated in 2016 under the sponsorship of the Surviving Sepsis Campaign.[79] These guidelines recommend ventilator therapy using lung-protective approaches for septic patients who develop ARDS (defined by the Berlin criteria). The guidelines recommend target tidal volumes of 6 mL/kg and target mean airway pressures of <40 cm H_2O. The guidelines also recommend the use of alveolar recruitment maneuvers and higher levels of PEEP. The guidelines state that PEEP can be titrated using bedside measurements of compliance or using titration protocols based on oxygenation variables.

Kacmarek and coauthors[80] presented a randomized trial comparing lung-protective ventilation combined with alveolar recruitment maneuvers and lung-protective ventilation without alveolar recruitment maneuvers (Acute Respiratory Distress Syndrome Network Protocol) in *Critical Care Medicine,* 2016. This article is supplied as a full-text reprint accompanying some formats of *SRGS*. The study enrolled 300 patients and 200 were assigned to the experimental protocol. The analysis showed that ICU mortality and ventilator-free days were equivalent in the two groups, but that patients assigned to the experimental group had improved oxygenation and driving pressures. The authors concluded that alveolar recruitment is safe and effective for improving oxygenation in patients with ARDS.

Heinze and coauthors[81] provided a potentially useful method of conducting an alveolar recruitment maneuver and documenting the effect of the maneuver in a report in *Critical Care Medicine,* 2011. The authors reported a study of recruitment maneuvers guided by bedside measurement of functional residual capacity. They measured functional residual capacity based on levels of oxygen in the airway circuit at end-inspiration and end-expiration in a group of postcardiac surgery patients (N=59). After measuring functional residual capacity and an airway circuit disconnect, patients were randomized to receive an alveolar recruitment maneuver or return to standard lung-protective ventilation. The analysis showed that patients whose functional residual capacity fell to <94% of baseline at the time of the ventilator circuit disconnect had a significant increase in functional residual capacity after the recruitment maneuver, while the patients whose functional residual capacity was maintained near baseline had no change after the recruitment maneuver. Interpretation of these data is limited because these patients did not have ARDS according to standard criteria. The data suggested, however, that patients with unstable lungs will benefit from recruitment maneuvers and that patients with ARDS (whose lungs are usually unstable and prone to alveolar collapse after ventilator circuit disconnection for suctioning) would probably benefit from recruitment maneuvers.

Data on the durability of benefits of alveolar recruitment measures vary in patients with ARDS. Fan and coauthors[82] offered a systematic review of available data regarding recruitment maneuvers in the *American Journal of Respiratory and Critical Care Medicine*, 2008. The authors analyzed data from studies involving nearly 1,200 patients. Available studies all showed improved oxygenation after recruitment maneuvers were applied, but most studies also disclosed that the improvement was

transient. Adverse events were unusual, although arterial hypotension accompanied most recruitment maneuvers. Hypotension was observed more often in patients with less severe lung injury. PEEP elevations after a recruitment maneuver improved the durability of the improvement in oxygenation. The authors cautioned that the value of transient improved oxygenation observed after recruitment maneuvers is currently unknown. Demonstrable impact of recruitment maneuvers on global outcomes measures, such as mortality, has not been demonstrated. They urged that the decision to employ recruitment maneuvers be based on the severity of respiratory distress (less severely hypoxemic patients probably do not benefit) and the response of the individual patient to PEEP and recruitment maneuvers. The least improvement in oxygenation was observed in patients with low-lung compliance. This might indicate that such patients have limited capacity for alveolar recruitment.

PEEP is frequently used to prevent the collapse of damaged alveoli during ventilator therapy for ARDS. Progressively higher levels of PEEP may contribute to the overdistention of alveoli and produce pneumothoraces. Determining the best approach to the use of PEEP in individual patients is challenging and requires frequent bedside adjustments of PEEP. A systematic review by Briel and coauthors[83] that evaluated higher PEEP levels vs. lower PEEP pressures for the management of patients with ARDS appeared in *JAMA,* 2010. The authors found three acceptable trials that included nearly 2,300 patients. Control groups received tidal volumes of 6–8 mL/kg and PEEP to achieve near normal oxygenation with plateau airway pressures of less than 30 cm H_2O. The higher PEEP group's plateau pressures were maintained at 40 cm H_2O with PEEP increased to achieve near normal oxygenation. Analysis of the trials' results showed that there was a small reduction in overall mortality associated with use of higher levels of PEEP and that higher levels of PEEP were potentially harmful in patients who did not have severe ARDS. These results need to be interpreted cautiously because two of the included trials were stopped before full enrollment because of futility, which may have been perceived because of the inclusion of patients in the trials who did not have severe ARDS.

Bedside ultrasound imaging has been used to document the effectiveness of alveolar recruitment with the use of PEEP. This approach was evaluated in an article by Bouhemad and coauthors[84] in the *American Journal of Respiratory and Critical Care Medicine,* 2011. In this study, the authors evaluated 12 lung regions using bedside ultrasound imaging and compared ultrasound evidence of increased alveolar aeration in response to PEEP with alveolar recruitment measured by pressure-volume curves. Thirty patients were evaluated at two levels of PEEP (0 and 30 cm H_2O). The analysis showed that ultrasound was as accurate as the pressure-volume curve for determining the effectiveness of alveolar recruitment, but imaging was not accurate in identifying alveolar overdistention. The authors concluded that ultrasound imaging was feasible and safe but that it should not be the only method used to identify recruitment effectiveness and the presence of alveolar overdistention.

Another ventilation strategy for patients with severe ARDS is high-frequency oscillatory ventilation. This modality is used frequently in premature infants with respiratory distress. Ventilation of the lung occurs due to rapid administration of very small tidal volumes (1–3 mL/kg) delivered at high ventilatory rates that allow for gas mixing within the lung so that oxygenation is preserved and carbon dioxide is removed. High-frequency oscillating ventilation allows for high-end-expiratory lung volume maintenance without overdistention of alveoli. The effectiveness of high-frequency oscillatory ventilation was addressed in an article by Ferguson and coauthors[85] in the *New England Journal of Medicine,* 2013. The authors reported outcomes from a randomized controlled trial of high-frequency oscillatory ventilation in a group of 548 patients with ARDS diagnosed according to standard criteria. The study was halted after fewer than half of the planned enrollment of patients had occurred because the all-cause mortality in the experimental group was 47% compared with a mortality of 35% in the control group. The authors concluded that there was no evidence of benefit from the use of high-frequency oscillatory ventilation in patients with ARDS.

In an editorial that accompanied this article, Malhotra and Drazen[86] cautioned that the available trials that show no benefit of high-frequency oscillatory ventilation are limited because of patient mix (varying proportions of

patients with homogeneous, suitable lungs and patients with heterogeneous, unsuitable lungs), varying patient sedation practices, and varying responses of protocols to hemodynamic instability observed during ventilator therapy. Malhotra and Drazen urged that research on the use of varying ventilator strategies continue so that more can be learned about the patterns of lung damage due to ARDS. It is hoped that, in the future, protocols of ventilator therapy can be applied more accurately according to the pattern of lung damage in individual patients.

The main objectives of lung-protective ventilation are to preserve adequate oxygenation, maintain lung inflation, facilitate re-inflation of contracted or collapsed alveoli, and minimize the risk of ventilator-associated lung injury. Continuous positive airway pressure strategies are well suited to these objectives. The limitations of continuous positive airway approaches include the facts that usage of these approaches requires an alert, cooperative, and spontaneously breathing patient; also these approaches are sometimes difficult to apply in intubated patients. A relatively small proportion of ICU ventilators can deliver continuous positive airway pressure efficiently. Thus, continuous positive airway pressure is most useful during the "liberation" or "weaning" process, as the patient is assisted through the transition from ventilator support to normal breathing. One variant of continuous positive airway pressure, airway pressure release ventilation (APRV), can be used in intubated patients. The patient must be breathing spontaneously in order for this mode of ventilation to work properly. In suitable patients, APRV can maintain lung inflation and recruit additional alveoli in the dependent areas of the lung during spontaneous breathing intervals.

An article describing APRV was by Habashi[87] in *Critical Care Medicine*, 2005. Habashi stated that APRV was initially described in two articles by Stock and Downs[88, 89] in 1987. This approach to ventilation uses continuous positive airway pressure (P_{high}) to maintain lung inflation for a preselected interval (T_{high}). Carbon dioxide elimination is facilitated by scheduling periodic releases of airway pressure that permit airway pressure to fall to a preselected level (P_{low}). Low pressure is maintained for a preselected interval (T_{low}) and carbon dioxide is eliminated by this exhalation. Spontaneous, patient-generated breaths assist in recruiting alveoli with diaphragmatic contractions. The recruited alveoli are in the dependent lung areas adjacent to the diaphragm. Habashi explained that the process of alveolar recruitment proceeds along variable time courses because inflation of one group of alveoli affects the inflation rate of neighboring alveoli. Recruitment, therefore, proceeds in a wave or "avalanche" fashion. Maintenance of continuous positive airway pressure assists in maintaining inflation as additional alveolar units open. Recruitment occurs because of decreases in pleural pressure rather than increases in airway pressure. Habashi emphasized that the intermittent airway pressure releases also work to prevent lung overdistention. To minimize de-recruitment, low pressure intervals are kept as short as possible (0.2 to 0.8 seconds in adults).

APRV contrasts with pure continuous positive airway pressure breathing in that work of breathing increases with continuous positive airway pressure alone because of the need for the patient to expend energy to remove carbon dioxide. In patients with decreased lung compliance and respiratory muscle deconditioning, this increased work of breathing might not be tolerated by the patient; APRV effectively addresses this problem. Habashi stated that alveolar ventilation is intermittent, while carbon dioxide delivery to the alveolus is continuous. The intermittent pressure releases refresh alveolar gas and reestablishes the gradient for diffusion of carbon dioxide from blood to alveolar gas. Oxygenation improvement during APRV occurs because of the maintenance of high mean airway pressure that serves to increase the number of ventilated, perfused alveoli. Spontaneous breaths during the high-pressure interval serve to recruit additional alveoli in the dependent, perfused lung areas and this mechanism assists in supporting oxygenation as well. Resistance of the artificial airway during the early phase of the pressure release interval provides airway resistance that effectively produces PEEP, which also assists in supporting oxygenation. Because of the PEEP that results from airway resistance, the low-pressure setting is preferably zero.

Initial setup of APRV is dependent on whether the patient is newly intubated or whether this modality is being used to assist in the transition to weaning. For example, an adult patient newly intubated would have a desired plateau airway pressure selected (20–35 cm H_2O) and this would be the high-pressure setting. Higher pressures might be required where combined lung and chest

wall compliance are reduced (obese patients). Low pressure would be set at zero. The high time interval would be set at 4–6 seconds and the low time interval would be 0.2–0.8 seconds. Longer low time intervals may be required in patients with COPD. These settings would produce 10–12 exhalations per minute. In patients who are transitioning from conventional ventilator support, the high pressure is set at the prior ventilation mode plateau pressure.

According to Habashi, APRV is a useful ventilation mode for spontaneously breathing patients who are ventilated in the prone position or in kinetic beds. The addition of pressure support ventilation to APRV produces unfavorable increases in transpulmonary pressure. Spontaneous breathing is required for effective use of APRV and, therefore, this approach is not indicated in patients who require aggressive sedation/analgesia or neuromuscular blockade. The modality is associated with less patient discomfort from the use of adjuvant ventilation compared to conventional ventilation. This consistent observation suggests that intervals of heavy sedation use or neuromuscular blockade might be shortened by applying airway pressure release ventilation. Habashi's conclusion indicates that weaning from APRV is a simple process involving reductions of the high pressure setting and extension of the high-pressure time interval. Decreasing the number of releases as the pressure changes are made facilitates the transition to normal patient breathing. This modality, according to Habashi, can be applied using noninvasive ventilation interfaces.

Comparative clinical data documenting the benefit of APRV are found in a review by Siau and Stewart[90] in *Clinics in Chest Medicine*, 2008. The authors observed that clinical series evaluating APRV have been retrospective observational studies or comparative studies employing historical controls. These studies suggested a reduction of mortality with the use of this modality in traumatic lung injury patients. There has been little control of confounding variables in these analyses and, because of this, a definite reduction in mortality cannot be assumed. Reductions in ICU lengths of stay as well as ventilator intervals have been reported. Direct comparisons of APRV to lung-protective ventilation have not been reported. Siau and Stewart concluded that while APRV is appropriate for carefully selected patients, a recommendation for the widespread use of this approach cannot be made based on current evidence.

As mentioned earlier, an area where APRV may be valuable is in patients who need a transition between conventional ventilation and the implementation of a formal "weaning" protocol. Weaning from ventilator support is clinically challenging. During full ventilator support, respiratory muscle deconditioning occurs and, because of this, muscle weakness might limit ventilatory effort. Lung and chest wall compliance are decreased by the primary lung disease as well as body habitus (obesity) and pain due to incisions, chest drainage tubes, and rib fractures. Successful weaning requires that the primary disease causing ARDS be under control. Also, the patient should be capable of initiating spontaneous breathing efforts. Ideally, the use of sedation and analgesia are reduced to the point that the patient can cough, make deep-breathing efforts, and participate in patient care by changing their position in the bed or moving from their bed to a chair with assistance. Nutritional deficits should also be corrected. Once these conditions are met, transition to an assisted ventilation strategy is a first step. Spontaneous breathing trials can be scheduled three or four times daily under nurse and/or respiratory therapist supervision and intervals of spontaneous breathing can be incrementally increased ("wind sprints"). When extubation is possible, noninvasive interfaces can be used to assist patients with "graduation" to normal breathing. These approaches are particularly useful in COPD patients.

Burns and coauthors[91] provided a systematic review of available data on the use of noninvasive ventilation as a weaning adjunct in the *British Medical Journal*, 2009. The authors reviewed 12 trials involving 530 patients. Most patients enrolled in weaning trials using noninvasive ventilation were COPD patients; however, COPD was not necessarily the main contributor to the need for ventilator support in the reported trials. Pooled data suggest a reduction in mortality and ICU length of stay for patients with COPD weaned with noninvasive ventilation protocols. There was no increased risk of weaning failure, pneumonia, or reintubation in the reported trials. The authors concluded that the evidence in support of

noninvasive ventilation as a means of facilitating weaning is sufficiently strong to recommend this modality in patients with COPD.

Editorial Comment

Weaning critically ill surgical patients from mechanical ventilation is highly dependent on the success of efforts to control the process that led to the need for ventilation in the first place. Deconditioning is an especially challenging problem that limits successful weaning in the elderly and in patients with severe comorbid conditions. Failure of weaning, with deterioration of oxygenation and lung compliance leading to reinstitution of ventilation, is a high price the patient pays for suboptimal timing of weaning. Weaning failure and extubation failure resulting in the need to reinstitute mechanical ventilation are, in my view, largely avoidable complications. Underestimation of the need for analgesia/sedation, underuse of assistive exercise physical therapy programs, inadequate patient counseling, delay or nonuse of nutritional support, and suboptimal level of consciousness are common modifiable factors contributing to weaning failure. Educating nurses, physical therapists, and respiratory therapists in the use of weaning protocols permits weaning and extubation when criteria for acceptable patient-controlled breathing are fulfilled. Use of these multidisciplinary protocols can improve the success rates for weaning in critically ill surgical patients.

Adjuncts to Mechanical Ventilation for Patients with ARDS

Several adjuncts to traditional ventilator therapy might improve ARDS outcomes in carefully selected patient groups. These adjuncts can be grouped as measures that help accomplish the following goals:

- Reduce the risk of additional lung injury (fluid therapy)
- Modulate the inflammatory process (corticosteroid therapy)
- Modify pulmonary hypertension (nitric oxide)
- Improve the distribution of ventilation and perfusion (prone positioning)
- Improve patient comfort to facilitate efficient ventilation (sedation, neuromuscular blockade, and anxiety reducing measures)
- Replace lung function (extracorporeal membrane oxygenation)

Pipeling and Fan[92] reviewed adjuncts for managing ARDS patients in *JAMA,* 2010. The authors observed that several of the reported therapeutic approaches to patients with ARDS have improved oxygenation, but only lung protective ventilation has been reported to improve survival. Data cited by the authors confirm a small (9%) risk reduction for mortality in patients with ARDS. Improved survival has been reported in some trials of early neuromuscular blockade in patients with severe ARDS. The authors acknowledged that these trials are limited by the varying definitions of severe ARDS and the fact that oxygenation is a poor surrogate for ARDS severity; only 10%–15% of patients with ARDS die from refractory hypoxemia. Instead, ARDS patients die from the failure of organs *other* than the lung.

Pipeling and Fan next discussed the use of prone positioning in treating patients with ARDS. Available data have not shown a survival benefit from this therapy. Guerin and coauthors'[93] report on a European randomized trial of prone positioning in the treatment of ARDS was published in the *New England Journal of Medicine,* 2013. In this study, 237 patients were randomized to receive standard ventilator therapy with 16-hour sessions of prone positioning daily. Patients had to have their first session of prone positioning within one hour of randomization. Patients were eligible for the study if they had ARDS (defined by standard oxygenation indices) and had been receiving ventilator therapy for less than 36 hours. The control group received optimum ventilator support without prone positioning. The results of the study showed significant decreases in 28-day and 90-day all-cause mortality when prone positioning was used. The authors stressed the importance of a protocol approach to prone positioning using a well-trained and coordinated team.

The benefits observed in the prone-positioning patient group may have resulted from long prone-positioning sessions and/or enrolling patients with severe ARDS of short duration; this patient group would be more likely to die from refractory hypoxemia than other causes. Pipeling and Fan concluded that prone positioning is a beneficial therapy for selected patients with ARDS.

Therapies such as permissive hypercapnia and prone positioning require careful monitoring of patient pain and discomfort. Analgesia and sedation are always necessary for most ARDS therapies to be effective. Practice guidelines sponsored by the American College of Critical Care Medicine were published in 2013.[94] The guidelines recommend consideration of epidural analgesia as a complement to systemic analgesia and sedation. They also recommend daily sedation interruptions. In addition, the guidelines offer a weak recommendation for the use of nonbenzodiazepine sedation (propofol or dexmedetomidine) rather than midazolam or lorazepam because of data suggesting that nonbenzodiazepine sedation is associated with improved outcomes in critically ill patients who require ventilator support.

Fraser and coauthors[95] conducted a systematic review of the literature that focused on the sedation of ventilated ARDS patients; their article was published in *Critical Care Medicine,* 2013. The authors identified six acceptable trials that included nearly 1,300 patients. The use of nonbenzodiazepine sedation was associated with significant reductions in ICU stays and in the duration of needed ventilator support. An important factor differentiating this analysis from previous studies is the exclusion of cardiac surgery patients. The authors cited data showing that durations of ventilator support are, on average, much shorter in this patient group and that the inclusion of cardiac surgery patients may obscure the benefit of nonbenzodiazepine sedative drugs. The authors also emphasized that the shorter half-lives of the nonbenzodiazepine sedatives facilitates the use of sedation-interruption protocols that may also contribute to shorter lengths of stay and durations of ventilation. It is also noteworthy that the midazolam is metabolized via cytochrome p450 and all of the benzodiazepine drugs are eliminated through the kidneys; the half-lives of these sedatives may be prolonged in critically ill patients. The authors also acknowledged that their analysis is limited by the heterogeneity of approaches to ventilator therapy and the lack of consistent protocols for sedation and sedation interruption in the studies they included. They recommended that additional studies of nonbenzodiazepine sedation be conducted and they concluded that their analysis supports the guideline recommendations from the Society of Critical Care Medicine.[94]

Recognition of the role of inflammation in the pathophysiology of ARDS has stimulated evaluation of anti-inflammatory strategies for ARDS treatment. This topic was the subject of a report by Tang and coauthors[96] in *Critical Care Medicine,* 2009. This report was a meta-analysis of randomized controlled trials and observational studies of low-dose corticosteroids (0.5–2.5 mg/kg/day) in patients with acute respiratory distress syndrome. For cohort studies, analyses of data drawn from 307 patients were included. Randomized trials included 341 patients. Both types of studies demonstrated improved mortality risk and both types of studies demonstrated improved oxygenation and decreased ICU lengths of stay. Overall, there was a 38% reduction in risk of death for patients treated with low-dose methylprednisolone. There was no increased risk of infection, neuromyopathy, or major complications in the steroid-treated groups.

The authors stated that their study effectively deals with the challenges faced by other investigators who attempted to determine whether there was a benefit to corticosteroid treatment with no increase in complications. Prior analyses dealt with widely varying dosage ranges, differing types of steroid drugs, and heterogeneous patient groups. This study dealt with studies using low-dose medication with standard definitions of ARDS and standard reporting of outcomes. The authors conducted subgroup analysis that indicated an efficacy of low-dose corticosteroids, even when treatment was started several days after the onset of ARDS. In addition, treatment effect was independent of the use of "open lung" ventilation strategies. The analysis also confirmed that the treatment effect was independent of any effect on the outcome of sepsis. The authors concluded that low-dose steroid treatment is effective and safe in patients with ARDS. The data indicate that steroid therapy should be tapered and

not stopped abruptly. Abrupt cessation of steroids can be associated with rebound inflammation and worsening of lung function.

Tang and associates acknowledged that their study was limited by the fact that they had no knowledge of the presence or absence of dysfunction of the pituitary-adrenal axis in these studies. An approach to the diagnosis of adrenal insufficiency in critically ill patients was the topic of a consensus report by Marik and coauthors[97] in *Critical Care Medicine*, 2008. The authors advised that the diagnosis of adrenal insufficiency in critically ill patients can be established by documenting an increase of less than 9 μg/dL of total serum cortisol following a dose of adrenocorticotrophic hormone of 250 μg, or a random total serum cortisol level of <10 μg/dL. Once the diagnosis is established, treatment with corticosteroid replacement is valuable, especially in patients with septic shock and inadequate responses to fluids and vasoactive drugs. Steroid therapy is useful in the treatment of early ARDS—confirming the observations of Tang and coauthors, discussed earlier. Readers should heed that the treatment benefit observed by Tang and colleagues was not limited to early ARDS.

While the study by Tang and coauthors[96] was well done, problems with heterogeneity and publication bias remain problematic in making a judgment with regard to the available data. A more recent systematic review by Horita and coauthors[98] in *Internal Medicine,* 2015, failed to confirm a benefit of corticosteroids for ARDS treatment after making thorough statistical adjustments to account for heterogeneity and publication bias.

Pipeling and Fan[92] stated that inhaled nitric oxide is a therapy designed to improve pulmonary hypertension and reduce the ventilation-perfusion mismatching that is ubiquitous in patients with ARDS. This therapy has not been associated with improved survival but may be useful in selected patients with pulmonary hypertension. The authors concluded by considering extracorporeal membrane oxygenation and lung transplantation approaches for patients with severe ARDS. Several studies have shown improved six-month, disability-free survival in patients randomized to receive extracorporeal membrane oxygenation. Some of these patients go on to receive a lung transplant and long-term survival is good in this select subgroup. Pipeling and Fan indicated that it is difficult to sort out the specific benefit of extracorporeal membrane oxygenation and lung transplantation from the overall better results achieved in centers that are capable of providing these advanced interventions. They emphasized that available data show that survival is improved in patients referred for extracorporeal membrane oxygenation, even though a number of patients referred for this therapy never receive the intervention.

Two reviews of data relevant to the use of extracorporeal membrane oxygenation have shown that the available technology and techniques of use have improved and this modality is feasible and relatively safe. From the available data, it is apparent that a clear-cut improvement in mortality from ARDS has yet to be demonstrated.[99, 100]

A simpler approach to extracorporeal lung support is extracorporeal interventional lung assist. This approach uses a low-resistance arteriovenous shunt. The patient's cardiac output drives blood through a membrane device that maintains oxygenation and removes carbon dioxide. The lungs remain inflated and ventilated with very low tidal volumes during the treatment interval. This approach was discussed in a review by Cortes and coauthors[101] in *Current Opinion in Anesthesiology,* 2012. This therapy, according to the authors, has shown encouraging results in small observational studies and will probably be most effective if used in combination with other approaches to improve oxygenation and carbon dioxide removal.

The final group of adjunctive interventions reviewed involve management of the airway; two components of airway management will be discussed. Lascarrou and coauthors[102] focused on the use of video laryngoscopy during endotracheal intubation; their article appeared in *JAMA,* 2017. The authors reported results of a randomized prospective trial conducted in seven ICUs in France. According to the authors, video laryngoscopy has become popular because of the clear view of the larynx provided by the instrument. Small observational studies have suggested that this clear view may be associated with improved results of intubation. In the trial reported, patients who required endotracheal intubation were randomized to be intubated using a video laryngoscope or with a conventional laryngoscope with a standard Macintosh blade. All intubations were conducted by

supervised trainees and intubation protocols (including preoxygenation and neuromuscular blockade) were used in all patients. The main outcome measure was successful first-pass intubation. Secondary outcomes included time to successful intubation and occurrence of moderate or severe complications. The trial enrolled 371 patients. The data analysis showed that rates of first-pass intubation were equivalent in the two groups (67%). Moderate and severe complications were seen significantly more frequently in the video laryngoscope group. The authors concluded that intubation success is not improved compared with conventional intubation techniques and that use of the video device is associated with an increased risk of complications. In an editorial that accompanied the article, O'Gara and coauthors[103] pointed out that the video laryngoscope indeed does provide a very clear view but that this can lead the intubating physician to spend time attempting to intubate when signs of hypoxemia emerge. In addition, data cited by the authors confirmed that use of the video laryngoscope is associated with difficulty visualizing the endotracheal tube as well as injury to the soft tissues of the pharynx, since the view of the pharyngeal anatomy is obscured during use of the video instrument. Based on the data reviewed, there seems to be no clear advantage to using video laryngoscope for intubation of patients in the ICU.

Percutaneous dilational tracheostomy has been used with increasing frequency since the safety and practicality of this bedside procedure has been confirmed. Tracheostomy is an adjunctive treatment used in patients with ARDS. The objective of tracheostomy use is mainly to improve patient comfort, permit speech, reduce the risk for laryngeal injury, and facilitate enteral nutrition. Available data suggest that tracheostomy facilitates discharge of patients from the ICU, shortens ventilator intervals, and possibly reduces the frequency and severity of VAP.

Unfortunately, these potential benefits are accompanied by costs and complications. Tracheostomy, at a minimum, results in disfiguring scarring of the anterior neck. Airway bleeding, tracheal ring fracture, tracheal stenosis, and esophageal injury might also occur. Tracheal-innominate artery fistula is another complication that has nearly disappeared with reductions in posttracheostomy local wound infection and appropriate choice of the level of tracheostomy tube insertion (third tracheal ring). Bedside percutaneous tracheostomy techniques have reduced the need to transfer patients to the operating room for formal surgical procedures. Overall reductions in health care resource utilization have been reported with the use of bedside percutaneous tracheostomy. Bedside tracheostomy requires partial removal of the endotracheal tube and use of the flexible fiberoptic bronchoscope for guidance of tracheostomy tube insertion. Thus, additional costs are incurred, along with the risk of sudden airway loss during the procedure.

Trouillet and coauthors[104] reported a retrospective observational study comparing postcardiac surgery patients with severe respiratory failure who were treated with percutaneous dilational tracheostomy immediately after intubation vs. long-term oral intubation; this article was published in *Annals of Internal Medicine,* 2011. Both groups were similar in clinical characteristics and severity of pulmonary failure. There was no difference in hospital survival or long-term survival when the groups were compared. The number of ventilator days was similar in the two groups. The patients who underwent percutaneous tracheostomy had less usage of analgesia and sedation and fewer episodes of unintentional extubation. These patients were also able to resume oral nutrition sooner. The authors concluded that while early tracheostomy has benefits in terms of patient comfort and well-being, these do not translate into improved outcomes for mortality and long-term quality of life.

A randomized trial comparing early vs. late percutaneous tracheostomy was described in an article by Young and coauthors[105] in *JAMA,* 2013. The authors reported outcomes from a group of patients (N=1,032) randomized to receive early percutaneous tracheostomy (within four days of intubation) or late tracheostomy (more than 14 days after intubation). Of note is that 92% of patients randomized to early tracheostomy received the procedure, while only 44% of the late tracheostomy group actually had the procedure performed. Many of the instances of nonperformance of the tracheostomy were the result of improvement in respiratory failure to the point that ventilator therapy was no longer needed. When the groups were compared for mortality, number of ventilator days, and length of hospital stay, there were no significant differences observed. In an accompanying editorial, Angus[106]

emphasized that these data should stimulate clinicians to adopt protocols that consider percutaneous tracheostomy for patients who require ventilator support for more than 14 days and who are not able to be weaned because of continued severe lung failure.

Percutaneous dilational tracheostomy usually includes the use of flexible bronchoscopy to provide documentation of a safe tracheal puncture, confirmation of guidewire placement, and observation of tracheostomy tube positioning. Recently, ultrasound imaging has been suggested as a means of providing this guidance. Gobatto and coauthors[107] described a randomized, prospective noninferiority trial comparing these two approaches in *Intensive Care Medicine,* 2016. The authors randomized 118 patients, with 60 patients assigned to the ultrasound arm of the study. The endpoint was a composite of procedure failure, need to convert from bronchoscopy or ultrasound to the other modality, and patient mortality. The data analysis showed that the composite outcome occurred with equal frequency in both groups and the requirements for determining noninferiority were met. Minor complications occurred more frequently in the ultrasound group, but the difference was not statistically significant. The authors concluded that ultrasound imaging was feasible, safe, and of potential value as an approach for monitoring the progress of percutaneous tracheostomy.

Editorial Comment

Early tracheostomy facilitates the care of certain types of injured patients. This patient group consists mainly of patients with moderate-to-severe brain injury who can be expected to survive and, perhaps, recover brain function over time. Tracheostomy may facilitate transfer of such patients to rehabilitation facilities or to assisted care facilities. The reductions in ICU lengths of stay and hospital lengths of stay reported in the articles discussed above support this conclusion. This patient group is also at increased risk for pneumonia, and tracheostomy may improve the diagnostic process for pneumonia; by reducing aspiration of secretions, pneumonia risk may be reduced. The reasons for decreased length of ventilator support reported by some authors in patients undergoing tracheostomy (especially early tracheostomy) are not clear. Reductions in airway-related complications and pneumonia risk may contribute to such reductions.

In this editor's experience, clinical judgment can usually determine, with acceptable accuracy, those patients who will likely require prolonged ventilator support. In this patient group, early tracheostomy is likely to have its greatest benefit. Percutaneous tracheostomy is the most efficient procedure and this approach is, in the experience of this editor, associated with the shortest interval of interruption of ventilator therapy. The available data, and clinical experience, have shown that providing consistent open-lung ventilation (discussed in the previous section) with minimal interruption of ventilation will maximize the likelihood of weaning and recovery of lung function—so long as the process producing ARDS can be adequately controlled and VAP can be avoided. Percutaneous dilational tracheostomy permits maintenance of ventilation during the procedure. In my view, tracheostomy facilitates a VAP diagnosis using bronchoalveolar lavage. I have consistently observed less supine positioning and more frequent suctioning of patients with tracheostomies. Patients with tracheostomies are repositioned in bed more frequently and are easier to move from bed to chair compared to patients with endotracheal tubes.

Ventilator-Associated Pneumonia

While ventilator support is a major contributor to successful management of ARDS, complications of this intervention do occur. One of the most feared complication of ventilator support is VAP. Bouadma and coauthors[108] focused on this topic in *Current Opinion in Infectious Disease,* 2012. The authors defined VAP as pneumonia that has its onset at least 48 hours after beginning ventilator support. The condition is caused by microbial invasion of the normally sterile lower respiratory tract and lung parenchyma. Microaspiration of contaminated oropharyngeal secretions from around the endotracheal tube is thought to be a major component of the pathogenesis of this condition. The highest risk for VAP is within the first

five days after intubation and recognition of this fact has led to early weaning and extubation efforts (wean protocols and sedation interruption) as a means of preventing VAP. Early tracheostomy has also been suggested as a method of VAP prevention. Data cited by the authors do not support early tracheostomy as an effective means of preventing VAP.

Bouadma and coauthors discussed data relevant to the use of silver-coated endotracheal tubes to help reduce the formation of contaminated biofilms. Available data are not strong enough to recommend this approach for VAP prevention; however, data do support the use of endotracheal tubes, which permit subglottic suctioning for effective VAP prevention. Damas and coauthors[109] conducted a randomized prospective trial of intubation with endotracheal tubes that permit subglottic suctioning; this report appeared in *Critical Care Medicine,* 2014. The trial included 352 patients admitted to ICUs in a single hospital. All patients were intubated with endotracheal tubes that permitted subglottic suctioning and were then randomized to either receive subglottic suctioning or not. The data analysis confirmed a significant reduction in VAP incidence in the group that underwent subglottic suctioning.

Other measures, such as elevation of the head of the bed and chlorhexidine oral decontamination, were discussed in the article by Bouadma and coauthors.[108] Data are available that suggest that these interventions are helpful VAP preventive measures. Available data have also supported the use of probiotics to reduce gastrointestinal colonization with pathogens that might cause VAP. The authors concluded by noting that there have been studies supporting the use of VAP care bundles for the prevention and management of this condition.

Croce and coauthors[110] evaluated the effectiveness of a care bundle for preventing and managing VAP in injured patients in the *Journal of Trauma and Acute Care Surgery,* 2013. The article reported a prospective study conducted in six Level 1 trauma centers in the United States. Frequencies of VAP, duration of ICU care, and mortality were recorded and compliance with the care bundle was determined on a daily basis. The data analysis did not confirm a benefit of care bundle use on VAP frequencies in this group of injured patients. VAP risk was significantly associated with male gender and the severity of chest injury.

VAP treatment using systemic antibiotics is chosen based on local antibiograms and/or culture results. ICUs have been documented to be patient care areas where frequencies of multidrug resistant pathogens are common. Two articles by Lu and coauthors [111, 112] addressed whether nebulized antibiotics might provide an additional means of treating resistant organisms without increasing the risk of additional resistant pathogen development. These articles described prospective trials of nebulized antibiotics in VAP patients. The data from both studies showed that nebulized antibiotics were effective, especially against multidrug resistant organisms. Notably, the use of nebulized antimicrobials did not augment the risk of resistant organism emergence in the ICUs included in the studies.

AKI & Renal Failure

A consensus statement from the United States Preventive Services Task Force (USPSTF) analyzed the potential benefits and harms of routine screening of asymptomatic adults for evidence of renal disease;[113] this report was published in the *Annals of Internal Medicine,* 2012. According to cited data, population estimates suggest that 11% of adults in the United States have evidence of renal disease. Given this degree of health burden, the USPSTF conducted a systematic review of the literature to determine whether there was evidence to support any benefits of early discovery of renal disease and early institution of treatment. Additional analysis was done to estimate the potential harm of screening adults. The data reviewed showed that more than 90% of patients with clinical evidence of renal disease have hypertension. Nearly half of those affected had diabetes and/or atherosclerotic cardiovascular disease. Patient groups at an increased risk included women and African-American patients. There was no hard evidence available to support the value of routine screening of asymptomatic adults, regardless of age, unless an identified risk factor was present. No evidence was discovered that documented a risk of harm from screening, but the data confirmed that the chance

of significant renal disease in asymptomatic adults without risk factors is very small. The review concluded that routine screening cannot be recommended.

As an increasingly older population of surgical patients with multiple comorbid diseases present for surgical evaluation and treatment, it makes sense to consider the best method to assess at-risk patients for chronic renal disease. This topic was discussed in an older article by Graves and coauthors[114] in the *Mayo Clinic Proceedings,* 2008. The authors emphasized that the glomerular filtration rate (GFR) declines at a rate of approximately 1% per year (each year) after age 30. It is not surprising that older patients have diminished capacity to respond to renal injury, which begins with processes that reduce GFRs. It was also observed that increasing life span results in an increased opportunity for the development of diseases that contribute to chronic renal insufficiency. These include hypertension, atherosclerotic vascular disease, and diabetes. With increasing age, patients are exposed to potentially nephrotoxic agents, including medications like nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics. As patients age, the risk of developing malignant disease increases. Many patients with cancer will require treatment with potentially nephrotoxic chemotherapeutic agents. Additional, potentially nephrotoxic medications used in older patients include proton pump inhibitors that can be used to treat gastroesophageal reflux and radiographic contrast agents that can be used to diagnose and treat coronary artery disease and other conditions. The article continued with a discussion of the diagnosis of renal disease: traditional clinical measurements of renal function have relied on estimations of GFRs assessed by measuring creatinine excretion. GFRs can be assessed by measuring serum creatinine and urinary levels of creatinine using a 24-hour urine collection procedure. This technique is, however, tedious and time-consuming and the method is subject to errors resulting from inaccurate collection. Clinical assessments of glomerular function usually rely on serum creatinine level measurements. Creatinine excretion is linearly related to GFRs as long as creatinine production is stable and the volume of distribution of creatinine is normal. Abnormal renal function is usually diagnosed if the serum creatinine level is greater than 1.8 mg/dL. If the measured serum creatinine level has increased by 25%–50% over a known baseline level, renal insufficiency can be strongly suspected.

Creatinine is produced at a constant rate as a byproduct of muscle cell metabolism and is filtered by the glomerulus (this accounts for 90%–95% of excretion). Creatinine is also excreted by the distal renal tubule (5%–10% of excretion). The authors warned that pharmaceutical agents that block distal tubular secretion of creatinine (trimethoprim, cimetidine, cefoxitin, and flucytosine) may cause elevations of serum creatinine levels when the GFR is actually normal. The most common factors influencing the accuracy of a renal disease diagnosis using serum creatinine levels are abnormalities of creatinine production; these occur when muscle mass is diminished by the effects of age and/or malnutrition. When the volume of distribution of creatinine is altered by conditions that result in an increased extracellular fluid volume or of total body water (sepsis, fluid overload, congestive cardiac failure, hepatic failure with ascites), assessing the GFR using serum creatinine levels will become undependable.

Creatinine clearance and GFR can be estimated by formulas combining serum creatinine levels with other indices of creatinine excretion including age, gender, and body mass index. The oldest formula for estimating creatinine clearance was the Cockcroft-Gault formula published in 1976 and described in an article by Cockcroft and Gault[115] in *Nephron,* 1976. The article provided a formula for creatinine clearance estimation that was developed from analyses of serum creatinine, age, and body weight in 249 patients. These patients ranged in age from 18 to 92 years. The results for creatinine clearance estimated by the formula were compared with the means of two 24-hour creatinine clearance measurements obtained in 236 patients. The authors reported that the formula had a strong correlation coefficient when compared with measured creatinine clearance for adult males. The formula gave similar correlation for women when the estimate for creatinine clearance obtained by the formula was adjusted downward by 15%. The original predictive formula equation suggested by Cockcroft and Gault was (C_{cr} = [140-age][wt in kg]/72 x S_{cr}[mg/100 mL]). The authors pointed out that because the bodyweight of an average-sized adult male approximates 72 kg, the number 72 appears in both the numerator and the denominator of the estimate formula if the patient resides in this group. Because of this, creatinine clearance expressed in milliliters per minute can be obtained, for such patients, using a simplified version of the formula, which is 140 minus the age of the patient divided by the serum creatinine

$\left(\frac{140 - age}{Cr_{serum}}\right)$. Cockcroft and Gault stressed the importance of including age in the predictive formula. Their data indicated that there is a linear decrease of approximately 50% in creatinine excretion expressed in milligrams per kilogram per 24 hours over the interval from the third to the ninth decades and that these results are similar to other published results in the medical literature. They emphasized that an understanding of the change in creatinine clearance with increasing age becomes very important when physicians must choose medications and adjust the dosage of medications. The hazard is described in this example: while a 30-year-old male might have the same serum creatinine as a 70-year-old male, their respective creatinine clearances will be significantly different. The authors further observed that creatinine clearance values obtained in paraplegic patients are low, probably because of muscle atrophy. Falsely low values for creatinine clearance are also obtained in obese patients and in patients with ascites, possibly because of a change in the volume of distribution for creatinine. The authors emphasized that creatinine clearance values in these patient groups should be corrected to ideal lean body weight. The article concluded with the important observation that the formulas estimating creatinine clearance assume that creatinine production and the general metabolic state of the patient are stable. For these reasons, predictive formulas for creatinine clearance and GFRs become undependable in states of acute illness and critical illness.

Fernandez-Prado and coauthors[116] provided a valuable discussion of the limitations of GFR prediction formulas in the *American Journal of Medicine,* 2016. The authors emphasized that the increased use of drugs such as NSAIDs and direct acting anticoagulants that require dosage adjustments based on renal function means that accurately assessing renal function will become more and more important. Similarly, the increasing number of older patients with significant comorbid conditions that require elective or urgent/emergency surgical procedures will cause future increases in the frequency of critical illnesses and renal injury risks. A GFR is the most accurate measurement used to diagnose and estimate the severity of renal damage. Because the direct measurement of GFR using creatinine clearance determined from serum creatinine and urine creatinine from a 24-hour urine sample is tedious and time-consuming, estimating GFRs using various formulas has been incorporated into clinical practice. The available formulas estimate creatinine clearance using variables such as serum creatinine, body weight, and ethnicity. The authors pointed out that using two different formulas for the same patient may yield two different GFR estimates. According to data cited in the article, recommendations for a renal damage diagnosis were given as creatinine clearance <30 mL/min or GFR <30 mL/min. The authors emphasized that creatinine clearance is not equivalent to a GFR because of tubular secretion of creatinine; also, a GFR is usually expressed as mL/min/1.73 M^2 to account for body surface areas. The authors concluded by stating that available clinical practice guidelines recommend using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for drug dosage adjustment. This formula uses serum creatinine, patient age, gender, and ethnicity to estimate GFRs. From the data presented, it is clear that the chosen means of assessing the risk of and/or determining the presence and severity of renal damage will require a GFR estimate that is accurate and can be applied across various patient groups.

Graves,[114] in the review of the diagnosis and management of chronic kidney disease, suggested that the four-variable predictive formula for creatinine clearance offered by the modification of diet in renal disease program (MDRD) is particularly valuable for clinicians because it is available on the Internet and only requires clinicians to insert values for variables such as serum creatinine, age, gender, and bodyweight. The formula can be found at *mdrd.com*. One possible disadvantage of using the MDRD assessment formula is the risk of overdiagnosing high-grade renal disease. This topic is discussed in an editorial by Kalantar-Zadeh and Amin[117] in *Annals of Internal Medicine,* 2012. MDRD assessment for chronic renal disease has been used to document the frequency of chronic renal disease in adults at 10%–12%. Patients with severe reductions of GFR (<60mL/min/1.73M^2) are classified as stage 3 or higher chronic renal disease; these patients have increased cardiovascular disease complication and death risks. Data cited by the authors suggest that stage 3 chronic renal disease is the largest category of renal disease diagnosed by the MDRD assessment; they stressed that this finding is counterintuitive. Additional

data cited in the editorial suggests that classification of renal disease using the method suggested by the CKD-EPI formula is a more accurate means of quantifying risk and stratifying patients. Using the CKD-EPI formula, nearly 30% of patients classified as stage 3 or higher chronic renal disease were reassigned to lower stages, where risks of mortality and complications were significantly lower. The authors suggested that the CKD-EPI formula, supplemented by the use of biomarkers such as cystatin C, may evolve as the most accurate means of stratifying risk in patients with chronic kidney disease.

The article by Graves[114] provided additional information about cystatin C and explained that cystatin C is an endogenous cysteine protease inhibitor produced, in most humans, at a constant rate by all nucleated cells; this substance is freely filtered by the kidney and is unaffected by renal tubular reabsorption or secretion. The two disadvantages of this surrogate GFR marker are that serum levels are more variable than those for creatinine and serum levels can be affected by acute disease (malignancy, infection with human immunodeficiency virus) and other, as yet to be determined, influences. This has left serum cystatin C measurements without a defined role in clinical medicine.

Graves emphasized that a precise GFR measurement can be obtained with radioisotope clearance studies. These are used, for the most part, to determine GFRs in patients who are believed to be candidates for chronic hemodialysis. As a general rule, hemodialysis is considered in patients with GFRs of 60 mL per 1.73 m^2 or less. In addition, the onset of uremic symptoms may also indicate the need for precise GFR measurements so that timely institution of chronic hemodialysis can occur. The author concluded by noting that none of these measurements are particularly helpful in assessing patients with acute deterioration of renal function.

The review went on discuss the steps for establishing the presence of and the extent of chronic renal disease. Graves stressed the importance of a careful history and physical examination. The history will, in many instances, disclose clues to the presence of such renal diseases as glomerulonephritis and interstitial nephritis. The history and physical examination will also provide information that assists in confirming the presence of correctable causes of renal insufficiency such as obstructive uropathy and prerenal azotemia. Causes of obstructive uropathy include intrinsic origins (e.g., renal stones, tumors, and papillary necrosis). Extrinsic causes of obstructive uropathy include benign prostatic hypertrophy, retroperitoneal fibrosis, and retroperitoneal tumors. Important adjuncts to the diagnosis of objective uropathy include the measurement of postvoiding residual bladder urine and renal ultrasonography. Renal ultrasonography is important as a diagnostic methodology because the images obtained provide information necessary to delineate obstruction at the ureteropelvic junction, ascertain kidney size, and provide color-flow arterial images that can establish the presence of renal artery stenosis. Graves indicated that an uncommon cause of postrenal insufficiency is renal vein thrombosis, a condition that is much more common in children than adults. When the condition occurs in adults, it is most often because of a blood coagulation disorder (usually associated with malignancy). The history and physical examination can also be helpful in diagnosing prerenal azotemia. A history of nausea, vomiting, and/or diarrhea will suggest extracellular fluid volume depletion as a cause of renal insufficiency. In addition, the unexpected resolution of long-standing edema, new or increased use of diuretics, weight loss, and orthostatic symptoms are helpful clues. The history can also suggest chronic heart failure, liver disease, and the nephrotic syndrome. Supine and standing blood pressure and pulse determinations are important components of the physical examination in such patients. Graves stated that an additional adjunct to diagnosing prerenal azotemia is determining the fractional excretion of sodium. In typical prerenal azotemia, the fractional excretion of sodium is less than 1%. The fractional excretion of sodium can be calculated with a standard formula using measured levels of urine and serum sodium and creatinine. The formula and a calculator can be found at *www.mdcalc.com/fractional-excretion-of-sodium-fena*.

It is worth stating that, in some instances, fractional excretion of sodium can be falsely low, suggesting prerenal azotemia when this condition is not the actual cause of elevated serum creatinine. Patients with glomerulonephritis, myoglobinuric renal failure, radiographic contrast media associated nephropathy, renal allograft rejection, acute interstitial nephritis, and recent diuretic treatment will have a falsely low fractional excretion of sodium.

Graves continued the discussion with a description of the types of intrinsic renal failure. He explained that there are three tissue types within the kidney: glomerular tissue, which is the site of primary glomerular disease, secondary glomerular diseases from other conditions (such as systemic vasculitis, diabetes, hypertension, and amyloidosis); vascular tissue that may be affected by systemic vascular disease, atheroemboli, and thromboembolism; and interstitial tissues, which can be damaged by sickle cell anemia, chronic analgesic use, and certain medications (antibiotics, proton pump inhibitors, and NSAIDs). Graves suggested that an accurate diagnosis can be achieved with four pieces of supplemental information: findings on urinary microscopy, results of a 24-hour protein excretion test, the presence of arterial hypertension, and the time course of elevated serum creatinine level.

In a discussion of the diagnostic value of urine microscopy, Graves indicated that the presence of red blood cell casts is an important indicator of intrinsic renal disease and emphasized that to be certain of an accurate identification of red cell casts, microscopic urine examination needs to occur within 20 minutes of urine specimen collection. He also stated that the presence of abnormal red blood cells is a common surrogate for the presence of red blood cell casts. Red blood cells that have traversed the glomerular basement membrane to reach the urinary space (as in glomerulonephritis) have a distorted appearance because of that transit. In contrast, red blood cells entering the urine from other parts of the urinary tract will not be distorted. Graves stated that although the use of this surrogate is accepted practice, careful evaluation shows that distorted red blood cells are no more suggestive of glomerulonephritis than undistorted red cells if there is substantial proteinuria. The author also discussed the 24-hour protein excretion test: in patients with glomerular disease, this test is at least 3.5 g/dL/1.7 3 M^2 body surface area—but can be much higher. Although substantial proteinuria is often associated with vasculitis, proteinuria is more pronounced in primary glomerular forms of renal disease. Interstitial renal disease usually presents with little or no proteinuria, but up to 2 g of urinary protein, primarily Tamm-Horsfall protein, may be excreted daily. The author explained that when vasculitis of the kidney is left untreated (especially with diseases such as Goodpasture syndrome, Wegener granulomatosis, and lupus vasculitis), the elevation of serum creatinine rapidly progresses to renal failure levels, reaching end-stage renal failure requiring dialytic support within weeks or months of the beginning of the disease. The author also pointed out that although untreated glomerulonephritis may have a rapid course, renal failure usually develops more slowly, with low GFR levels reached in a period of 2 to 10 years. Interstitial renal disease has an even more indolent course, reaching low GFR levels only after 10 to 20 years. Rapidly increasing serum creatinine level is possible with allergic interstitial nephritis and acute tubular necrosis.

Graves next discussed measures for preserving renal function in patients with evidence of chronic kidney disease: the mainstays of therapy for preserving renal function are aggressive blood pressure control, control of diabetes mellitus, reductions in low-density lipoprotein cholesterol, and the avoidance of nephrotoxins, particularly medications and radiographic contrast media.

Editorial Comment

It is clearly important for surgeons to maintain a high index of suspicion for the presence of renal disease and for signs of renal dysfunction, especially in elderly or critically ill patients requiring urgent or emergency surgical care. Whenever possible, assessments of a prior history of renal dysfunction, including examination of records to discover previous measurements of serum creatinine and, if available, GFR estimates, might provide valuable clues for identifying patients at risk for a perioperative deterioration of renal function. Where significant risk of renal disease exists, interventions to prevent and treat extracellular fluid volume depletion and measures to avoid exposure of the patient to nephrotoxic substances are indicated.

Acute Renal Dysfunction in Surgical Patients

There is a clinical importance in monitoring acute changes in renal function, particularly as this condition affects patients who are critically ill. The term "acute kidney injury" has replaced the traditional diagnostic term "acute tubular necrosis" because of the recognition that renal

injury is present along a continuum of severity, with renal failure being just one stage of this continuum. Furthermore, acute tubular necrosis as a diagnosis implies the need for a histologic confirmation. Renal biopsy for histologic examination is frequently impractical in critically ill patients. According to a review article by Waxman and Holmes[118] in *Surgical Clinics of North America,* 2012, traumatic injury, sepsis, and septic shock were the most common clinical conditions contributing to the development of acute renal failure in patients cared for by general surgeons.

The epidemiology of AKI was reviewed in an article by Bellomo and coauthors[119] in *Lancet,* 2012. The authors cited data confirming an incidence of 5,000 cases per million population for nondialysis requiring renal insufficiency and an incidence of 295 case per million population for severe renal insufficiency requiring dialysis. In developing countries, hypovolemia from diarrhea is a common cause of renal insufficiency. In developed countries, AKI is more often observed in hospitalized patients following open cardiac operations; critically ill patients with sepsis from pneumonia or peritonitis are particularly vulnerable to AKI.

Clinical Definitions of Acute Kidney Injury & Renal Failure

Bellomo and colleagues stated that AKI is diagnosed when abnormalities of excretion of creatinine and urea and/or decreased urine output are present. A consensus conference promoted by the Acute Dialysis Quality Initiative agreed on a continuum of renal injury severity defined by five stages: risk, injury, failure, loss, and end-stage kidney disease (RIFLE criteria). The various stages are determined by GFR estimates—using serum creatinine levels to estimate GFR. Reductions in urine output over time in intervals of 6, 12, and 24 hours are also used to define the RIFLE stages. Srisawat and Kellum[120] illustrated the RIFLE stages in an article in *Current Opinion in Critical Care,* 2011. A similar staging system has been suggested by the Acute Kidney Injury Network (AKIN). This system defines three stages of AKI based on increases in serum creatinine, the time course of the change in serum creatinine, and decreased urine output. This staging system broadened the definition of "failure" and placed more emphasis on the time course of the rise in serum creatinine rather than the absolute increase. Srisawat and Kellum indicated that these changes improved the sensitivity of an AKI diagnosis. In their review, Waxman and Holmes[118] cited data that suggest an increased risk of progression of AKI with increases in serum creatinine of 10%–24% rather than the 50% rise recommended by the RIFLE and AKIN staging systems. They also emphasized the lack of precision associated with use of these staging systems and emphasized the need for more accurate diagnostic criteria.

Waxman and Holmes[118] observed that the development of AKI is associated with an increased risk of in-hospital mortality and morbidity. AKI may also adversely affect the function of other organ systems. For example, the authors cited data indicating an increased risk of prolonged mechanical ventilation in patients with AKI and concurrent pulmonary insufficiency. Organ "cross-talk" is one factor that may help to explain the apparent impact of AKI on distant organs. This topic was examined in an article by White and coauthors[121] in the *Journal of Surgical Research,* 2011. The authors reviewed available evidence in the literature and suggested that the activation of the inflammatory cascade and the resulting elaboration of mediators by the innate and adaptive immune systems are the most likely mechanisms of damage to distant organs in patients with AKI associated with sepsis. The authors cited data confirming that increased elaboration of cytokines and other mediators precedes the development of AKI and dysfunction of distant organs. Although additional confirmatory data are needed, this mechanism is likely to have a major impact on sepsis-associated organ dysfunction. Additional evidence of the association of clinical evidence of AKI and multiple organ failure was presented in a report by Wohlauer and coauthors[122] in the *Journal of Trauma and Acute Care Surgery,* 2012. The authors reviewed medical record data on more than 2,000 patients admitted to the ICU of a Level 1 trauma center. Early evidence of AKI (defined as a serum creatinine level of 1.8 mg/dL) was observed within two days of admission in 2.1% of patients. The authors documented a statistically significant association of early evidence of AKI and subsequent development of multiple organ failure. A significant association of AKI and mortality was also

confirmed. The authors hypothesized that early evidence of AKI is an indicator of a systemic process being initiated that ultimately will lead to multiple organ failure.

Risk factors for AKI were discussed in an article by Siew and Deger[123] in *Current Opinion in Nephrology and Hypertension,* 2012; the authors observed that advanced age, male gender, diabetes, and African-American ethnicity have been identified as AKI risk factors. The severity of an associated illness has also been linked to an increased risk. One particularly powerful risk factor is preexisting renal disease. The authors emphasized that the discovery of proteinuria is an important clue in diagnosing preexisting renal disease. Although proteinuria is easily assessed on routine urinalysis, it is unclear whether this factor is modifiable by available interventions. Siew and Deger indicated that a full recovery of renal function was confirmed in the majority of patients who survive to hospital discharge. They cited data suggesting an increased risk of chronic renal insufficiency developing over long-term follow-up in patients who experience AKI.

Additional perspective on the risk of chronic renal insufficiency in patients with AKI was provided in an article by Rifkin and coauthors[124] in the *Journal of the American Society of Nephrology,* 2012. The authors examined available evidence of a causal relationship between AKI and chronic renal insufficiency using standard criteria for determining causality. They pointed out that causality is difficult to determine mainly because of the lack of confirmation of preexisting renal disease prior to an AKI diagnosis. Furthermore, because patients with a comorbid disease and an increased acute injury severity are likely to receive more intensive follow-up, there is a bias risk in diagnosing chronic renal disease in this high-risk group. The authors concluded that assigning a causal relationship between AKI and chronic renal insufficiency is not possible using currently available data.

Mechanisms of Renal Injury & Renal Failure

The traditional understanding of AKI and acute renal failure in surgical patients is based on experimental models of ischemic kidney injury. These models showed that hypoxic glomerular and tubular injury resulted in inflammation, activation of the coagulation mechanism, endothelial injury, and microvascular occlusion. Therapeutic strategies were recommended based on the understanding of AKI as a disorder caused by ischemia. These approaches emphasized preserving renal perfusion using intravascular volume expansion and pharmacologic agents, such as low dose dopamine. Kellum,[125] in an editorial in *Critical Care Medicine,* 2011, presented a succinct analysis of the relationship between reduced renal blood flow and the development of AKI. The evidence reviewed disclosed that a significant number of patients develop AKI when there is no history of hypotension. Furthermore, many patients with profound hypotension do not develop renal injury. He cited data from multiple experimental and clinical studies that showed no relationship between reduced renal blood flow and AKI from sepsis. The author cited data from randomized clinical trials that confirm that there is no benefit of using renal vasodilators to increase renal blood flow in patients with AKI. Kellum concluded that the relationship between reduced renal blood flow and AKI cannot be confirmed.

Confirmation of a meaningful clinical relationship between renal blood flow and AKI has been impeded by the lack of a valid method to measure, simultaneously, cardiac output and renal perfusion. Data from a small pilot study by Prowle and coauthors[126] in *Critical Care Medicine,* 2012, described an innovative and potentially useful method for assessing cardiac output and renal perfusion. The authors reported data from 10 patients with established AKI. They measured simultaneous cardiac output and renal perfusion using phase-contrast magnetic resonance imaging. They were able to obtain the studies even on critically ill patients requiring ventilator support. The data disclosed a significant reduction in the fraction of cardiac output delivered to the renal tissue in patients with AKI from sepsis. Rachoin[127] mentioned in an accompanying editorial that additional data will be needed to confirm the utility of this methodology, but that these preliminary results are encouraging.

The lack of a relationship between a reduction in total renal blood flow and AKI raises the possibility that intrarenal mediators are working to alter the delivery of nutrients and oxygen to renal cells. One such mediator is nitric oxide. The production of nitric oxide by renal endothelial cells is increased in experimental models of

sepsis. The effect of blockade of nitric oxide synthesis in a septic model was the focus of an article by Ishikawa and coauthors[128] in *Critical Care Medicine,* 2012. The authors reported data from an experimental study conducted in 12 sheep. Sepsis was induced by infusing live *E. coli* organisms intravenously. Data from measurements of renal blood flow as well as blood and urine chemistry studies were reported. During sepsis, a hyperdynamic circulatory state was confirmed and total renal blood flow was increased. Evidence of AKI was observed in results of blood and urine chemistry measurements. Renal blood flow was reduced by administering nitric oxide inhibitors, but this intervention had no effect on the chemical evidence of AKI. In an accompanying editorial, Anderson[129] indicated that a consensus on the role of nitric oxide in AKI has not been achieved, probably because of the varied experimental models used. He emphasized that the pathophysiology of AKI is likely to be complex, involving multiple mediators outside of and within the kidney. Additional data are needed to clarify the impact of these multiple factors.

Acute Renal Injury in Specific Clinical Settings

Two specific causes of acute renal injury, radiographic contrast-induced nephropathy (CIN) and abdominal compartment syndrome, will be discussed in this section.

Contrast-Induced Nephropathy

AKI from radiographic contrast media contributes to the health burden of this disorder. Data relevant to this topic were presented in a report by Rabanni and Nallamothu[130] in *Annals of Internal Medicine,* 2011. The authors cited data indicating that CIN is seen in 1%–2% of patients receiving contrast; this disorder accounts for as much as 10% of the cases of renal dysfunction in hospitalized patients. The most important risk factor for CIN is preexisting renal disease that can often be diagnosed by the presence of proteinuria. Other risk factors include the use of nephrotoxic drugs such as NSAIDs. Associated comorbid conditions such as diabetes, anemia, and congestive heart failure increase the risk for CIN. The authors recommended preventive measures such as low-osmolar contrast agents, periprocedural hydration, and low-dose procedural protocols. Preventive drugs such as N-acetyl cysteine have been widely used, but a recent randomized trial has provided data confirming no benefit with the use of this agent.

As discussed previously, the advancing age of the surgery patient population and the increasing use of contrast-enhanced radiographic procedures for diagnosis and therapy have amplified the importance of CIN. Because this complication is widely held to be iatrogenic and potentially preventable, vigorous efforts to identify pathways for effective prevention have been reported recently; these preventive measures are the topic of an older but still valuable article by McCullough[131] in *Critical Care Medicine,* 2008. The author began by stressing that acute renal failure occurring in critically ill patients is a major contributor to ICU mortality. McCullough affirmed that there are relatively few studies available that deal specifically with the complication of acute renal failure following contrast-enhanced radiographic procedures performed on critically ill patients. Because of this, McCullough chose to provide a detailed review of the reports from the CIN Consensus Working Panel. This panel identified 865 pertinent reports in the medical literature dealing with this complication; a systematic review was then performed to identify important factors in the epidemiology, pathogenesis, renal function assessment, risk assessment, high-risk patient identification, contrast medium use, and preventive strategies. After the completion of this literature review, a series of consensus statements was developed by the panel. The results were also used to formulate an algorithm to manage patients at risk for this complication. McCullough provided a clinical definition adopted by the panel: this definition included an increase in serum creatinine either in absolute terms (0.5 to 1.0 mg per dL) or as a proportional rise of 25% relative to baseline. The author stressed that the change in serum creatinine generally occurs within 24 hours of the radiographic procedures (but may occur at 48 hours) and the maximal elevation of serum creatinine occurs within five days of

the procedure. The consensus panel definition required that the change in serum creatinine occur within 48 hours of the time when the radiographic contrast material was administered. McCullough observed that the frequency of CIN has decreased over the past decade from a general incidence level of approximately 15% to a current level of approximately 2%–7%. This decline is probably due to a greater awareness of the problem, better risk prevention measures, and the use of less nephrotoxic contrast media.

To clarify the magnitude of the health burden of CIN, McCullough cited data confirming that radiographic contrast media-associated renal injury is the third most common cause of hospital-acquired renal failure. This condition was responsible for 11% of the total cases of AKI. A mortality rate of 14% was recorded in patients who developed this problem. McCullough cited two reports dealing specifically with critically ill patients. These two reports documented an incidence of 2% in patients without preexisting renal disease who received iodinated contrast. In the second report, which dealt with surgical ICU patients, the incidence was 1.4%. The study further indicated that 3.5% of the surgical ICU patients who developed renal failure requiring dialysis had received radiographic contrast media in addition to having another risk factor for acute renal failure. The author cited additional reports documenting the significant increase in mortality risk in patients who develop CIN. One report documented a 34% mortality rate in patients developing acute renal failure after contrast administration compared with 7% mortality in matched control patients who did not develop renal failure after contrast-enhanced radiographic procedures.

McCullough pointed out that early mortality risk is not the only adverse factor associated with CIN. Citing data from an analysis of patients followed for a minimum of one year after the development of CIN, the author presented evidence that the mortality rate at 12 months after an episode of renal failure after a contrast- enhanced radiographic procedure was 12% and this rose to 45% at five years. This would strongly suggest that the early mortality risk persists over the long term. This adverse mortality risk is particularly pronounced in patients who require long-term dialysis after developing CIN. In addition, the author pointed out that data are available linking this type of AKI with an increased risk of long-term severe cardiovascular events. As might be expected, CIN development leads to increased hospital stays and hospital costs; the average incremental increase in hospital costs for one episode of this type of AKI is $10,345.00.

The CIN mechanism is probably similar to the mechanisms of other vasoconstrictive injuries to the kidney. Also, because iodinated contrast media is water-soluble, it resides in the urinary space adjacent to the glomerulus and renal tubules and is directly cytotoxic to the cells in these tissues. Patients with preexisting depression of GFR are particularly vulnerable to CIN. The author cited several reports documenting that the risk of CIN is increased in patients with an estimated GFR of less than 60 mL per minute. This would be equivalent to a serum creatinine level of greater than 1.3 mg/dL. In elective contrast-enhanced radiographic procedures, a record of an estimated GFR using one of the conventional formulas (or at least a baseline serum creatinine) is a useful piece of information to obtain before the radiographic procedure so that protective measures can be provided. Obviously, older patients, diabetic patients, and patients with cardiovascular disease are candidates for a careful preprocedure evaluation of renal function. McCullough stressed that the toxicity of the contrast medium used for the radiographic procedure is related to the osmolarity. Several reports have indicated a lower AKI risk using low-osmolarity media. The author emphasized that there is solid evidence to support a conclusion that iso-osmolar or low-osmolar contrast media are associated with the lowest risk of AKI. When intraarterial contrast medium injection is contemplated, these media are preferred. When radiographic procedures requiring an intravenous contrast medium (such as contrast-enhanced CT scanning) are considered, a low-osmolarity contrast medium is preferred. Additional protection can be achieved by restricting the volume of the injected contrast medium to 100 mL or less. For patients with calculated GFRs that are abnormally low, the dose of contrast medium can be adjusted so that the maximum volume administered is no more than twice the estimated GFR in milliliters. The importance of contrast agent volume was emphasized in an article indicating that in patients undergoing percutaneous coronary interventions, contrast volume was related

to biochemical evidence of renal injury—even when hydration and iso-osmolar contrast media were employed as measures to prevent renal dysfunction.[132]

McCullough next considered preprocedure protective measures that are useful for patients at risk for CIN. The most dependable protective measure is adequate hydration during the periprocedural interval. Maintenance of an hourly urine output in excess of 100 to 150 mL an hour is preferred. Pharmacologic protection was achieved with the use of preprocedure theophylline in one controlled trial. The author agreed that N-acetyl cysteine, a popular drug used to protect against CIN, has not consistently shown benefit. The author concluded by noting that although contrast medium is efficiently removed by hemodialysis, there is no evidence to support prophylactic hemodialysis as a means of protecting patients against this complication.

Data published in a report by Kim and coauthors[133] in the *Journal of Trauma and Acute Care Surgery*, 2012, sought to determine the safety of intravenous contrast in one high-risk group: severely injured patients. The authors reviewed outcomes data on 571 patients without evidence of preexisting renal disease. All patients were severely injured and all had ICU stays >48 hours. Clinical evidence of AKI developed in 30% of patients. Multiple logistic regression analysis disclosed that advanced age and higher injury severity scores were risk factors for the development of acute renal injury. Exposure to radiologic contrast material was not a discrete risk factor. The authors believed that the use of a protocol-driven approach to optimize the safety of radiologic procedures was responsible for reducing the risk of CIN in these patients. The authors stated that they routinely optimized patient fluid status and hemodynamics and they routinely used low-osmolar or iso-osmolar contrast media. These data support the safety of indicated radiologic procedures when efforts to maximize safety are utilized.

Abdominal Compartment Syndrome

A second specific cause of renal injury is abdominal compartment syndrome. This syndrome is the result of persistent intraabdominal hypertension and has far-reaching systemic effects that are primarily a consequence of intraperitoneal organ edema and intraperitoneal fluid accumulation. This topic was discussed in an article by Roberts and coauthors[134] in *Current Opinion in Critical Care,* 2016. The authors stated that various injuries/conditions can lead to abdominal compartment syndrome, but that the common pathway includes intestinal ischemia-reperfusion injury (most often initiated as a result of shock and resuscitation). Nontrauma conditions that may produce abdominal compartment syndrome include ruptured abdominal aortic aneurysm, severe pancreatitis, peritonitis, and nontraumatic intraabdominal bleeding. Shock and resuscitation lead to increased bowel wall permeability with intestinal swelling and extravasation of fluid. Increased bowel wall permeability permits translocation of intestinal bacteria. The release of bacteria and bacterial products into peritoneal fluid produces a systemic response that can damage other organ systems, including the kidneys; normal intraabdominal pressure is 5–7 mm Hg. The authors recommended that abdominal pressure be assessed by measuring pressure at the level of the iliac crest via a bladder catheter with 25 mL of sterile saline within the bladder. The patient should be supine and pressure should be measured at the end-expiration phase of ventilation. Abdominal hypertension (IAH) is graded at four levels according to measured intraabdominal pressure. Overt abdominal compartment syndrome is diagnosed when grade III-IV IAH is confirmed (pressures exceeding 20 mm Hg). Data cited by the authors show that abdominal compartment syndrome may be observed in up to 12% of patients admitted to the ICU. Renal function impairment can occur because of increased pressure that reduces renal perfusion and because of the systemic response to shock and bacterial/bacterial products translocation.

Clinical evidence that may predict mortality or increased risk of renal failure was the focus of a retrospective, multi-center medical record review by Shaheen and coauthors[135] in the *Journal of Emergencies, Trauma, and Shock,* 2016. The authors reported outcomes data on 28 patients cared for in three Level 1 trauma centers in a single urban area. The data showed that persistent IAH >20 mm Hg was strongly predictive of mortality. Renal injury was predicted by elevated admission lactate levels and the need for an initial operation lasting more than two hours.

Intraabdominal hypertension at levels below 20 mm Hg may be treated with nonoperative measures (sedation, neuromuscular blockade, nasogastric decompression, catheter drainage of intraperitoneal fluid). Most surgical patients and all patients with IAH at pressures >20 will respond best to decompressive laparotomy and delayed abdominal wall closure. Outcomes of this approach were recorded in a prospective cohort study by De Waele and coauthors[136] in the *British Journal of Surgery,* 2016. Thirty-three patients were included in the analysis. Decompressive laparotomy relief of IAH in all patients and improved renal function in patients with preoperative signs of renal impairment was observed. Overall in-hospital mortality was 33% and one-year mortality was 55%. Mortality after decompressive laparotomy was due to the severity of the underlying disease—not complications of the procedure. According to the authors, abdominal closure and successful healing were facilitated by advanced wound care approaches, including the use of negative pressure dressings.

Diagnosing Acute Renal Injury

A review article by Ostermann[137] in *Current Opinion in Critical Care,* 2014, provided a useful update on the current status of diagnostic approaches for AKI. As noted in previous discussions, basing the diagnosis of kidney disease, including AKI, on measurements of serum creatinine and incorporating these into predictive formulas can cause delays in diagnosing and managing AKI in critically ill patients. Because AKI affects 13%–18% of patients admitted to intensive care and because AKI increases the risks of mortality, morbidity, and the use of health care resources, establishing an early and accurate diagnosis is important. The author pointed out that several definitions of AKI are available to clinicians: these include the RIFLE criteria (2004), the AKIN definition (2007), and the Kidney Disease Improving Global Outcomes (KDIGO) definition that was added in 2012 (Figure 7). Limitations to the accuracy of each of these definitions include the fact that all use measurements of serum creatinine. Ostermann emphasized that serum creatinine can be influenced by patient muscle mass and associated diseases such as cirrhosis. The change in serum creatinine necessary to comply with the KDIGO definition of AKI may require 24–36 hours to become apparent. Because of this, the risk of diagnostic delay is significant. The KDIGO criteria require an increase in serum creatinine of 0.6 mg/dL within 48 hours or an increase of 1.5 fold from baseline within seven days. Data cited by the author confirm that a significant proportion of proven instances of AKI occurred with serum creatinine changes of smaller magnitudes. Other markers used to diagnose renal dysfunction (e.g., levels of blood urea nitrogen [BUN], and fractional excretion of sodium [FENa]) are also subject to inaccuracies.

Gotfried and coauthors[138] presented a review of the diagnostic value of FENa and BUN to establish the presence and severity of AKI in the *Cleveland Clinic Journal of Medicine,* 2012. The authors observed that a euvolemic patient with normal renal function will have a FENa of 1%. Values lower than this suggest prerenal causes of renal dysfunction, while values higher than 3% suggest intrinsic renal disease or injury. Falsely low FENa can be observed in patients with renal injury due to rhabdomyolysis, renal artery stenosis, and hepatorenal syndrome. Falsely high FENa is observed in patients on diuretics who develop prerenal azotemia. The authors emphasized that the use of fractional excretion of urea (FEUrea) as a complementary test to FENa has improved diagnostic accuracy, especially in patients on diuretic medications. FEUrea can be calculated using serum and urine levels of urea nitrogen measured by standard laboratory analyses. A calculator to determine fractional excretion of urea can be found at *https://www.mdcalc.com/fractional-excretion-urea-feurea*. The authors provided a helpful table comparing the diagnostic accuracies of FENa and FEUrea. FENa and FEUrea calculations are not accurate predictors of important clinical outcomes, such as the need for chronic dialysis or mortality. Similarly, examining urinary sediment to determine the presence of renal tubular epithelial cells and/or coarse granular or mixed cellular casts has been used to differentiate patients with acute tubular necrosis from those with prerenal azotemia. Most of the available data suggest, however, that the presence of red blood cell casts and/or distorted red blood cells is the only accurately predictive urinary sediment finding indicating renal disease. Data cited by Ostermann[137] confirm that using FENa is not sufficiently accurate to determine the

Figure 7 Classification systems for AKI. Reproduced from Ostermann[137] with permission.

RIFLE, AKIN and KDIGO classifications for acute kidney injury

	Serum creatinine criteria			Urine output criteria of all classifications
	RIFLE classification	AKIN classification	KDIGO classification	
Definition of AKI		Increase in serum creatinine of either ≥0.3 mg/dl (≥26.4 μmol/l) or a percentage increase of ≥50% (1.5-fold from baseline) in 48 h	Rise in serum creatinine by ≥26 μmol/l over ≤48 h, or to ≥1.5-fold from baseline which is known or presumed to have occurred in the preceding 7 days	
Stage I or RIFLE Risk	Increase in serum creatinine to ≥1.5 to two-fold from baseline, or GFR decrease by >25%	Increase in serum creatinine by ≥26 μmol/l (>0.3 mg/dl) or increase to more than or equal to 1.5-fold to two-fold from baseline	Rise in serum creatinine by ≥26.5 μmol/l in 48 h, or rise to 1.5–1.9 times from baseline	<0.5 ml/kg/h for >6 h
Stage II or RIFLE Injury	Increase in serum creatinine to >two-fold to three-fold from baseline, or GFR decrease by >50%	Increase in serum creatinine to more than two-fold to three-fold from baseline	Rise in serum creatinine 2.0–2.9 times from baseline	<0.5 ml/kg/h for >12 h
Stage III or RIFLE Failure	Increase in serum creatinine to >three-fold from baseline, or to ≥354 μmol/l with an acute rise of at least 44 μmol/l, or GFR decrease by >75%	Increase in serum creatinine to more than three-fold from baseline, or to ≥354 μmol/l with an acute rise of at least 44 μmol/l, or treatment with RRT irrespective of the stage at the time of RRT	Rise in serum creatinine three times from baseline, or increase in serum creatinine to ≥353.6 μmol/l, or initiation of RRT irrespective of serum creatinine	<0.3 ml/kg/h for 24 h or more, or anuria for 12 h
RIFLE Loss	Complete loss of kidney function for >4 weeks	–	–	
End-stage kidney disease	End-stage kidney disease for >3 months	–	–	

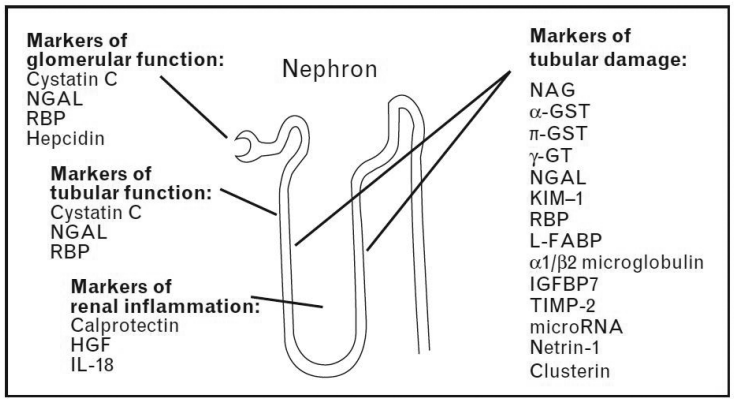
AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; GFR, glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcomes; RIFLE, Risk, Injury, Failure, Loss, End-stage; RRT, renal replacement therapy.

severity of and the need for clinical interventions in patients suspected of having AKI. Ostermann went on to emphasize that renal biopsy may provide accurate information regarding the presence of AKI, but this modality is rarely used in critically ill patients because of concerns about potential complications of the procedure.

Ostermann provided a useful review of data relevant to the use of biomarkers to diagnose AKI. Most of the data on the use of biomarkers focuses on neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, kidney injury molecule-1 (KIM-1), and IL-18. A diagram was included in the article that illustrates the various biomarkers and the locations of nephron damage that are indicated by each biomarker (Figure 8). The author stressed that biomarkers have been shown to provide an earlier diagnosis of AKI compared with measurements of serum creatinine in homogeneous patient groups. Accuracy is reduced in heterogeneous patient groups, such as patients encountered in the emergency department and in medical-surgical ICUs. Combinations of biomarkers

Figure 8

Biomarkers for AKI classified by the functional location within the nephron. Reproduced from Ostermann[137] with permission.



such as urinary TIMP-2 and IGFBP-7 have been studied and have shown sensitivities in excess of 90% for an AKI diagnosis; a commercially available point-of-care device (NephroCheck®) using these markers has become available, as confirmed in a brief report by Endre and Pickering[139] in *Nature Reviews-Nephrology,* 2014.

Waxman and Holmes[118] provided additional information on using biomarkers to diagnose and provide a prognosis in AKI patients. The authors explained that IL-18 is a proinflammatory cytokine that is thought to be indicative of proximal tubular cell injury. This cytokine can be measured in the urine. In renal transplant patients, it is an accurate means of assessing prognosis for long-term function in the engrafted organ. The authors did not comment on the availability of the assay. They agreed that NGAL is a useful diagnostic and prognostic biomarker. A newer biomarker, KIM-1, is a cell membrane glycoprotein that is only expressed in proximal renal tubular cells in response to injury.

Doi and coauthors[140] published a prospective clinical observational study of using biomarkers as diagnostic and prognostic tools in critically ill patients in *Critical Care Medicine,* 2011. The authors prospectively gathered data on 339 patients admitted to a mixed medical-surgical ICU. They assayed patient urine samples on admission to the ICU for L-type fatty acid binding protein, NGAL, N-acetyl beta-D glucosaminidase, IL-18, and albumin. Clinical evidence of AKI developed in 39% of patients. L-type fatty acid binding protein was the most accurate biomarker for diagnosing early and late-onset kidney injury, with an area under the ROC curve of 0.75. This finding suggests moderate sensitivity of the assay. This biomarker was also the most accurate predictor of prognosis, with an area under the ROC curve of 0.90, indicating strong performance as a prognostic indicator.

Acute Renal Injury Prevention & Nondialysis Therapy

Key elements in the successful prevention of renal failure are detection of preexisting chronic kidney disease, early recognition of AKI, aggressive treatment of underlying conditions such as peritonitis, and maintenance of normal volume status. It is critical that the surgical team be mindful of the effects of drugs and intravenous contrast agents on renal function. The most important factors under the control of the surgical team are recognition of volume deficits and restoration of normal blood volume and blood flow. The physiologic disturbances that accompany disease processes requiring surgical treatment contribute to preoperative deficits in blood volume and extracellular fluid volume. Volatile anesthetic agents may produce myocardial depression and reduced cardiac output. When these changes combine with the effects of the aforementioned preoperative deficits and the effects of intraoperative blood and fluid losses, the stage is set for renal injury to occur. The impact of acute renal failure on mortality risk, morbidity, and health care costs has served as a continuing stimulus to develop effective prevention strategies. The lack of precision in diagnosing renal injury and the limitations of clinical evidence as a means of tracking the progress of renal dysfunction has frustrated these initiatives. A number of promising pharmacologic agents have been investigated in animal models, but these have not consistently demonstrated clinical effectiveness in humans. Currently, the below actions are the most dependable means of preventing acute renal failure:

- Acquiring an accurate assessment of baseline renal function in each at-risk patient and maintaining accessible clinical information about risk factors for renal function impairment (atherosclerotic vascular disease, hypertension, dyslipidemia, advanced age, and diabetes)
- Maintaining adequate hydration
- Minimizing exposure to nephrotoxins
- Rapid assessment and goal-directed resuscitation of hemorrhagic hypotension and sepsis

Despite the shortcomings of preventive efforts so far, it is important for surgeons to be knowledgeable about agents that show promise for the future as well as strategies that have been documented as ineffective.

Practice guidelines for the management of AKI were published in 2012 by Khwaja[141] in *Nephron Clinical Practice.* The guidelines recommend conventional management of critical illness in patients with AKI. These measures include enteral nutrition, goal-directed management of hemodynamic instability, lung-protective ventilation for patients requiring ventilator support, avoidance of nephrotoxic drugs, and prevention of hyperglycemia and hypoglycemia. The guidelines state that there are no specific pharmacologic agents proven to prevent progression of AKI. Diuretics are not administered except in the setting of fluid overload.

Waxman and Holmes[118] presented a coherent strategy for AKI prevention. They emphasized the importance of a careful review of the medications that have been administered in the past and that are currently being used. The authors agreed that goal-directed fluid therapy protocols are valuable. They cited data indicating that positive fluid balance is associated with worse outcomes for critically ill patients with AKI and ARDS. The authors also provided additional data that support the use of conventional intravenous fluids and albumin. They recommended against the use of synthetic colloids based on recent randomized trial data cited in the article.

Yunos and coauthors[142] reported a randomized trial of reduced chloride intravenous fluid therapy (Hartmann's solution) compared with high-chloride fluids (normal saline and/or albumin); this article was published in the *Journal of the American Medical Association,* 2012. This "before-and-after" prospective study compared more than 750 patients in a control period with a similar number of patients in a study period. Patients in the study period were treated with the restricted chloride fluid regimen. The authors found that there was a significant reduction in the incidence of progressive AKI and the need for renal replacement therapy during the study period. Mortality rates were similar in the two study periods. The data reported could not identify a mechanism of the improved outcomes. In an accompanying editorial, Waikar and Winkelmayer[143] commented that the magnitude of the treatment effect (50% reduction in the use of renal replacement therapy) is difficult to explain given the lack of an effect on mortality. They acknowledged that the before-and-after model used in this study limits the interpretation of the data because of the potential for bias from the Hawthorne effect. While the study may be limited by this problem, there is support in the reported data for the use of reduced chloride intravenous fluids.

Waxman and Holmes[118] stated that erythropoietin has been recommended as an AKI treatment on the basis of the tissue protective and antiapoptotic effects of the drug. Waxman and Holmes cited data from a randomized trial that did not confirm improved outcomes in patients with AKI treated with erythropoietin. They emphasized that this trial had several important limitations, including weaknesses in the diagnostic approaches to AKI and definition of endpoints. As such, the conclusion that erythropoietin has no value is not conclusive. Other pharmacologic agents such as dopamine and fenoldopam are not recommended. The authors mentioned a small study that reported improved renal function after intravenous alkaline phosphatase was administered to critically ill patients with AKI. Additional data will be needed before a firm recommendation regarding the use of alkaline phosphatase can be made.

Renal Replacement Therapy

Current approaches to renal replacement therapy include intermittent hemodialysis, continuous renal replacement therapy, and peritoneal dialysis. In critically ill and postoperative patients, treating acute renal failure with peritoneal dialysis is not feasible.

The practice guidelines for AKI management[141] recommend instituting continuous or intermittent renal replacement therapy based on patient characteristics. Continuous therapy is especially well suited for patients at risk for hemodynamic instability. The guidelines recommend using percutaneous catheters placed in the right jugular vein as the first choice; the femoral site is recommended as the second choice. The guidelines recommend using anticoagulant therapy during renal replacement therapy sessions based on the patient's bleeding risk. Finally, the guidelines recommend discontinuing renal replacement therapy as soon as the indications for instituting therapy are no longer present.

Karvellas and coauthors[144] conducted a systematic review of the literature that examined data comparing early vs. late institution of renal replacement therapy; this article appeared in *Critical Care,* 2011. The authors examined 15 studies and determined that the quality of evidence supporting one approach to the timing of renal replacement therapy over another was low. Despite this, the authors indicated that the available data support a lower mortality and shorter intensive care and hospital stays in patients treated with early renal replacement therapy.

Another review of the literature addressed the question of intermittent vs. continuous renal replacement therapy. This analysis was by Ricci and Ronco[145] in *Current Opinion in Critical Care,* 2011. The authors explained that there is wide variability in the use of intermittent vs. continuous renal replacement therapy. Available randomized trials could not identify improved outcomes associated with the use of either form of renal replacement therapy. The authors stated that available evidence supports the use of continuous therapy in more severely ill patients, particularly those who are hemodynamically unstable. The choice of continuous renal replacement therapy should consider the impact of "down time" due to circuit clotting, operative procedures, and radiologic examinations. The "dose" of continuous replacement is expressed as mL/kg/hr; the optimum dose is 30 mL/kg/hr. The authors stressed that the removal of solutes such as urea can be accurately predicted when either intermittent or continuous renal replacement therapy is used. The removal of other substances such as cytokines and inflammatory mediators is possible using hemofiltration modalities.

Data from two additional articles[146, 147] suggested that the choice of renal replacement therapy is now made using decision processes similar to those used to choose modes of ventilation. Despite available data that show no improvement in survival with the use of continuous vs. intermittent renal replacement therapy, the use of continuous modes of renal replacement therapy is increasing in critical care units. The choice of continuous vs. intermittent therapy is made based on local expertise and availability of equipment to match the therapeutic approach to the needs of the patient. For example, continuous renal replacement therapy is better suited for critically ill patients who are at risk for hemodynamic instability. Patients who require intensive nutritional support are more likely to reach nutritional goals when managed on continuous renal replacement therapy protocols because fluid overload and azotemia can be continuously controlled. Continuous approaches will likely become more frequently used as technology improves the ability to remove toxins, cytokines, and other harmful substances while "useful" substances are preserved.

An article by Tolwani[148] in the *New England Journal of Medicine,* 2012, provided useful information about the potential advantages and disadvantages of continuous renal replacement therapy. The author explained that the clinical course of acute renal injury requiring renal replacement therapy can be divided into four phases: initiation, extension, maintenance, and recovery. Initial damage to renal tissue occurs during the initiation phase. Activation of inflammation and elaboration of cytokines within the kidney contributes to the extension phase. During this phase, additional renal damage occurs. GFR stabilizes during the maintenance phase and recovery begins during the final phase. The duration of the phases

varies from days to weeks. Renal replacement therapy is usually begun during the latter phases of initiation or during the extension phase.

Tolwani also discussed the processes of removal of fluid and solute during renal replacement therapy. Depending on the type of renal replacement therapy and the membranes used, removal occurs by ultrafiltration, diffusion, and convection. Fluid and small molecules are removed by ultrafiltration and larger molecules are removed by diffusion and convection. Ultrafiltration is a primary process used in both intermittent and continuous renal replacement therapy. Diffusion and convection are important components of hemofiltration.

The main disadvantage of intermittent hemodialysis in critically ill patients is the hypotension that can occur in up to one-third of patients. This disadvantage has led to an increased use of continuous approaches in patients at risk for hemodynamic instability. Although it is possible to remove cytokines and inflammatory mediators using hemofiltration, there is no evidence that hemofiltration alters the course or outcome of sepsis.

Vascular access for continuous renal replacement therapy is obtained, in most instances, using percutaneously placed central venous catheters. Other options include cuffed and/or tunneled central venous catheters. The catheter insertion site recommended most frequently is the internal jugular site because of data that indicate a lower risk of infection when this site is used. The subclavian insertion site is also commonly used in critical care; however, this site may be disadvantageous in the patient who is at risk for chronic hemodialysis, since subclavian central venous catheterization is associated with vein wall damage, which may lead to stenosis and lower success rates for chronic dialysis access procedures conducted on the same side as the subclavian catheter placement. Surgeons caring for patients who are at risk for chronic hemodialysis at a later time would be wise to limit, insofar as possible, central venous catheterization via the subclavian route on the side where a chronic access procedure may be planned.

Editorial Comment

It seems most useful to place central venous catheters in the internal jugular site in patients where the catheter is needed for continuous renal replacement therapy, since this site will serve to protect upper extremity venous drainage should chronic dialysis be needed. Where strict asepsis and catheter care protocols are followed, the femoral site is safe from the point of view of infection risk, especially in patients with a low BMI. Venous thrombosis is, however, a continuing hazard. The ultimate success of renal replacement therapy will be judged not only by short-term mortality rates and rates of renal recovery, but by long-term outcomes.

I hope that you have found this first issue of our surgical critical care series useful. Please feel free to share any comments or suggestions you may have. The second issue of the critical care series will deal with a variety of topics, including shock and transfusion management, ICU delirium, and outcomes of critical care.

Thanks for reading *SRGS*!

Lewis Flint, MD, FACS
Editor in Chief

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Posttest | CRITICAL CARE OF SURGICAL PATIENTS, PART I

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To earn self-assessment CME credit, the posttest MUST be completed online AFTER reading the literature review: *facs.org/publications/srgs/cme*. For more CME information, please see page ii.

1. National clinical practice guidelines for perioperative cardiovascular care define a "time-sensitive" procedure as one that can be delayed for how long?

a) 12 weeks
b) One year
c) 48 hours
d) Three months
e) 1–6 weeks

2. The national guidelines list each of the following as a risk factor for cardiovascular disease except which one?

a) Diabetes
b) Asian ethnicity
c) Hypertension
d) History of stroke
e) Frailty

3. A potential adverse event that may occur with the use of perioperative β-blocking drugs is which of the following?

a) Allergic reaction
b) Atrial fibrillation
c) Hypotension
d) Tachycardia
e) Polyuria

4. Data presented in the article by Andersson and coauthors indicate that perioperative β-blocker therapy may be beneficial in which patient group?

a) Patients with diabetes
b) Patients with hypertension
c) Patients with chronic renal failure requiring dialysis
d) Patients with a history of cardiac failure
e) Patients who are scheduled to undergo joint replacement

5. The report by Chopra and coauthors suggests that preoperative statin use in patients scheduled to undergo cardiac or vascular operations may improve which of the following?

a) All-cause mortality
b) Quality of life at six months after operation
c) Risk of postoperative myocardial infarction
d) Risk of postoperative pneumonia
e) Risk of ventricular arrhythmias

6. Data cited in the article by Devereaux and coauthors indicate that most postoperative myocardial infarctions occur within what time interval?

a) First 48 hours
b) 5–7 days
c) 14–21 days
d) In the third postoperative week
e) After 30 days

7. Postoperative elevations of troponin to levels below the threshold for diagnosing myocardial infarction are associated with which of the following?

a) All-cause 30-day and 180-day mortality
b) Preoperative history of coronary artery disease
c) Intraoperative hypoglycemia
d) Increased risk of postoperative supraventricular tachycardia
e) Increased risk of deep vein thrombosis

8. Following a fatal postoperative myocardial infarction, autopsy evidence of complete coronary artery occlusion is discovered in which percentage of patients?

a) 95%
b) 35%
c) 19%
d) 7%
e) 1.5%

9. Over long-term follow-up, which percentage of patients with diabetes mellitus will develop cardiac failure?

a) 60%
b) 3%
c) 72%
d) 34%
e) 15%

10. Data cited in the article by Kazaure and coauthors showed that potentially modifiable preceding events (sepsis, hypotension, renal insufficiency) occurred in which percentage of patients who sustained a postoperative cardiac arrest?

a) 2.5%
b) 7%
c) 35%
d) 14%
e) 66%

11. Estimates of the frequency of obstructive sleep apnea suggest that the condition exists in which percentage of American men?

a) 11%
b) 4%
c) 0.8%
d) 26%
e) 41%

12. Smoking cessation is beneficial for reducing the risks of postoperative respiratory complications if cessation occurs at which of the following times?

a) At least six months prior to operation
b) At least three months prior to operation
c) At least two weeks prior to operation
d) At least four weeks prior to operation
e) At least three days prior to operation

13. The Berlin definition of acute respiratory distress syndrome categorizes patients into three severity groups based on which of the following variables?

a) Levels of arterial carbon dioxide
b) Oxygenation
c) Lung compliance
d) Percentage of lung area with infiltrates on chest radiograph
e) End-expiratory percentage of oxygen in the ventilator circuit

14. The Berlin definition of acute respiratory distress syndrome defines "acute" as which of the following?

a) Clinical symptoms for 12 hours of less
b) Clinical symptoms for 24 hours of less
c) Clinical symptoms for 4 days or less
d) Clinical symptoms for 7 days or less
e) Clinical symptoms for 10 days or less

15. Data from the article by Blum and coauthors showed that risk factors for the development of postoperative acute respiratory distress syndrome included all of the following except which one?

a) Volume of electrolyte solution infused during the procedure
b) Number of episodes of general anesthesia during the index hospitalization
c) Preoperative renal failure
d) COPD
e) Female gender

16. The lung-protective ventilation protocol described in the article by Meade and coauthors used which of the following target tidal volumes?

a) 6 mL/kg
b) 16 mL/kg
c) 10 mL/kg
d) 3 mL/kg
e) 20 mL/kg

17. Glomerular filtration rates can be accurately measured by calculating creatinine clearance using creatinine levels from a 24-hour urine collection. This approach is frequently inaccurate because of which of the following?

a) Changes in creatinine production
b) Inaccurate collection of urine specimens
c) Erroneous timing of blood sampling
d) Unexpected changes in the volume of distribution of creatinine
e) Patient use of nonsteroidal antiinflammatory drugs

18. What percentage of creatinine is secreted by the distal renal tubule?

a) 95%
b) 60%
c) 5%–10%
d) 78%
e) 4%

19. The Cockcroft-Gault formula for calculating glomerular filtration rates was first reported in what year?

a) 1890
b) 1976
c) 2004
d) 2016
e) 1933

20. The protocol reported by Kim and coauthors for reducing the risk of contrast-associated renal injury emphasized which of the following interventions?

a) Low-dose dopamine infusion
b) Use of fresh-frozen plasma for volume expansion prior to administration of contrast
c) Use of low-osmolar or iso-osmolar contrast agents
d) Transfusion to hemoglobin levels of 14 gm/dL or higher
e) Administration of adenosine intravenously prior to the radiographic procedure

The following four questions are required by the American College of Surgeons for accreditation purposes. You must complete these four questions before submitting your answers.

21. This issue met the stated learning objectives.

a) Strongly agree
b) Agree
c) Neutral
d) Disagree
e) Strongly disagree

22. The content was relevant to my educational needs and practice environment.

a) Strongly agree
b) Agree
c) Neutral
d) Disagree
e) Strongly disagree

23. There are potential barriers to incorporating what I have learned from this issue into my practice.

a) Strongly agree
b) Agree
c) Neutral
d) Disagree
e) Strongly disagree

24. The content was fair, objective, and unbiased.

a) Strongly agree
b) Agree
c) Neutral
d) Disagree
e) Strongly disagree

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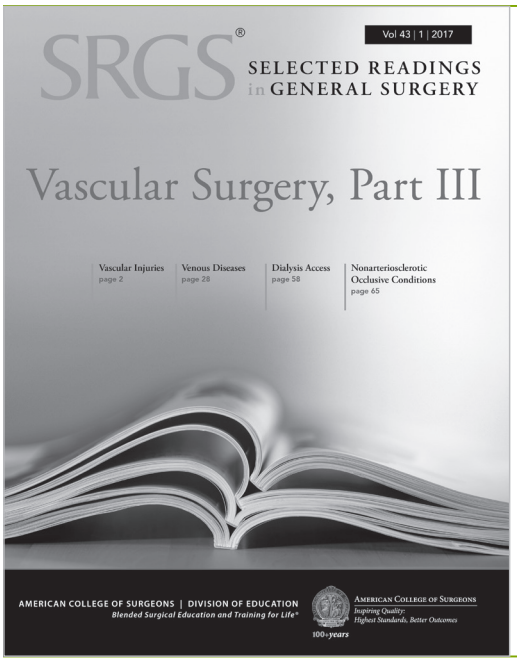

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Recommended Reading | CRITICAL CARE OF SURGICAL PATIENTS, PART I

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The *SRGS* Recommended Reading List is a carefully selected summary of current, classic, and seminal articles for further study. All of the articles below are cited in the order they appear in the literature review; they also appear in the reference list (57-62).

Full-text reprints of these articles are included in certain formats of *SRGS*.

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1. **Perioperative Management to Reduce Cardiovascular Events....70-75**

   Smilowitz NR, Berger JS

   This article presents a useful review of management principles for reducing the risk of perioperative cardiovascular events.

2. **Management of antithrombotic therapy in patients undergoing invasive procedures...76-87**

   Baron TH, Kamath PS, McBane RD

   Baron and coauthors review approaches for managing patients who are chronically anticoagulated.

3. **Risk factors of postoperative myocardial infarction after colorectal surgeries...88-94**

   Moghadamyeghaneh Z, Mills SD, Carmichael JC, Pigazzi A, Stamos MJ

   This report investigates risk factors for myocardial infarction following colon and rectal procedures. Not surprisingly, operative complexity contributed to increased risk.

4. **Chest compression alone cardiopulmonary resuscitation is associated with better long-term survival compared with standard cardiopulmonary resuscitation...95-101**

   Dumas F, Rea TD, Fahrenbruch C, et al.

   This study confirms the value of compression-only cardiopulmonary resuscitation.

5. **Postoperative pneumonia-prevention program for the inpatient surgical ward...102-106**

   Wren SM, Martin M, Yoon JK, Bech F

   This study describes a pneumonia prevention protocol and offers data supporting its feasibility and possible effectiveness.

6. **Open Lung Approach for the Acute Respiratory Distress Syndrome: A Pilot, Randomized Controlled Trial...107-117**

   Kacmarek RM, Villar J, Sulemanji D, et al.

   This study provides important data regarding the use of lung-protective ventilation.

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