

### Introduction

Tremendous morbidity remains associated with coronary artery disease (CAD) in surgical patients. Perioperative myocardial infarction is still often lethal and may compromise a patient's functional status after surgery. Patients who suffer postoperative myocardial infarction may on average incur \$10,000 - \$20,000 in additional hospital costs compared to similar patients who do not suffer myocardial infarction. Attempts to improve perioperative outcome of patients at risk for having CAD have focused on 3 approaches: (i) preoperative identification of high-risk patients who might benefit from myocardial revascularization, (ii) improved detection of perioperative myocardial ischemia to allow for prompt therapeutic intervention, and (iii) the prophylactic use of anesthetic and antiischemic techniques to decrease the prevalence and severity of postoperative myocardial ischemia. This lecture will address the last two approaches after reviewing the pathophysiology, demographics, and prognosis of postoperative myocardial ischemia and infarction in patients undergoing noncardiac surgery. Many of studies referenced have been undertaken in vascular surgery patients.

### Myocardial Ischemia Vs. Myocardial Infarction:

Myocardial ischemia is the surrogate that is more often addressed in the research reviewed in this lecture. To demonstrate reductions in the rate of infarction (typically reported at ~ 5% in vascular surgical series) with a therapy would require thousands of patients and millions of dollars to show statistically differences. We are beginning to see multi-center trials in the anesthesia literature, the use of meta-analysis to combine the results of trials by different investigators of similar interventions, and the analysis of large databases and registries to evaluate therapies.

### Predictors And Prognosis:

**Demographic predictors (prior probability).** Risk factors may include known CAD, congestive heart failure, peripheral vascular disease, advanced age, severely limited exercise tolerance, chronic renal insufficiency, uncontrolled hypertension and left ventricular hypertrophy, and the use of digoxin. Evidence of decompensated heart disease, such as arrhythmias or CHF, appears particularly associated with adverse outcomes. Multifactorial indices, such as Goldman's index, have been proposed to risk-stratify patients. Other investigators have proposed that specialized preoperative testing, such as Holter monitoring or thallium scanning, is much more accurate than clinical indicators for predicting perioperative cardiac complications. L'Italien et al have derived a multifactorial index derived from both clinical and thallium scintigraphy data which can be adapted to different clinical settings. Lee et al recently determined preoperative predictors of adverse cardiac events after noncardiac surgery in a large cohort; these predictors include previous MI, CHF, cerebrovascular disease, major surgery, and diabetes treated with insulin. Resting echocardiographic indicators (systolic dysfunction) may also have additive predictive value (above and beyond clinical risk factors) for predicting perioperative myocardial infarction in high-risk patients.

**Dynamic postoperative predictors.** Factors that may increase the likelihood of postoperative myocardial ischemia that we can control include tachycardia, anemia, hypothermia, shivering, hypoxemia, endotracheal suctioning, and less-than-optimal analgesia. For patients undergoing noncardiac surgery, perioperative MI may be associated with higher postoperative heart rates and higher pain thresholds, but not necessarily angina (most are silent). Other factors, such as postoperative hypercoagulability, and REM sleep rebound are more speculative culprits.

**Prognosis.** Postoperative myocardial ischemia confers increased risk to surgical patients. The Study of Perioperative Ischemia (SPI) group detected ischemic ST-segment changes in 20% of patients before surgery and in 41% afterwards. Postoperative myocardial ischemia increased by 9-fold the risk of an in-hospital morbid cardiac event. Landesberg et al found that ischemia that lasted > 2 h was associated with a 32-fold increase in the risk of morbid cardiac events. Both groups showed that postoperative myocardial infarction is usually preceded (by more than 24 hours) by long periods of severe ST segment depression. We believe that patients with documented severe postoperative myocardial ischemia should be referred to a cardiologist, since they are at high risk for adverse long-term cardiac outcomes. Perioperative MI is still associated with 20-30% in-hospital mortality, and is a marker for poor prognosis after discharge in those who survive.

**Detection of Myocardial Ischemia and Infarction:**

Patients undergoing vascular surgery are most likely to manifest myocardial ischemia in the immediate postoperative period, usually on the day of surgery or the next. The "silent" nature of postoperative ischemia suggests that frequent ECG monitoring may be useful. We believe that such a strategy may detect ischemia that is severe and protracted enough to represent a prodrome to infarction and focus on the period when MI is most likely to occur. Charlson et al found that obtaining a 12 lead ECG on the day of surgery and the next two days was the best strategy for detecting perioperative ischemia and infarction. Unfortunately, approximately 1/4 of vascular surgery patients will have baseline ECG abnormalities (LBBB, paced rhythm, digoxin effect, LVH with strain) that preclude the detection of myocardial ischemia. Other techniques of ischemia detection, such as the presence of v-waves in the PCWP tracing or decrements in regional wall motion detected with TEE, are less useful after surgery because they are discontinuous, expensive, and relatively invasive. Troponin levels appear more specific in detecting perioperative myocardial infarction than CK-MB isoenzyme measurement; troponin elevations are associated with lower survival after vascular surgery.

**Proposed Mechanisms Of Postoperative Myocardial Ischemia:**

Stable ischemic syndromes presumably occur with increased oxygen demand on the myocardium in a setting of fixed coronary plaques. Unstable syndromes are thought to be the result of plaque rupture with local thrombus and vasoreactivity that produce intermittent critical decreases in coronary oxygen supply. Patients with elevated coronary calcium on CT scan have greater rates of perioperative MI after vascular surgery. Endothelial function is impaired in CAD, hypertension, hypercholesterolemia, diabetes, and tobacco abuse, resulting in exaggerated vasoconstriction. Poor endothelial function is also associated with poor outcome after vascular surgery. Treatment to "heal" the endothelium (often with statin drugs) improves perioperative outcome, though effective therapy may have to begin weeks before surgery. Also, in patients with left ventricular hypertrophy (LVH), diminished coronary vasodilator reserve results in poor subendocardial perfusion. Early postoperative ischemia is usually associated with ST segment depression rather than ST elevation. ST segment depression usually precedes postoperative cardiac complications. Most perioperative MIs are of the non-Q wave variety.

The postoperative period is characterized by adrenergic stress, which can induce myocardial ischemia in patients with CAD; cause coronary vasoconstriction, and facilitate platelet aggregation. Tachycardia limits diastolic time and coronary perfusion, and it can paradoxically reduce coronary artery diameter. Hypertension and tachycardia in the PACU have been shown in a large study to be associated with increased mortality and unplanned ICU admission (although association does not necessarily mean causation.)

Surgery can induce a hypercoagulable response due to increased platelet number and function, diminished fibrinolysis, decreases in natural anticoagulants (including protein C and antithrombin III), and increases in procoagulants (including fibrinogen, factor VIII coagulant, and von Willebrand factor). These postoperative changes may contribute to an increased likelihood of coronary thrombosis in the postoperative period, but their relative importance in predicting postoperative coronary events remains speculative.

Cardiologists and internists are increasingly undertaking aggressive long-term pharmacologic risk reduction in patients with CAD. These strategies include cholesterol reduction with statins, which stabilize coronary plaques, antihypertensive therapy with ACE inhibitors, which also reduce sympathetic tone, and "tighter" glucose control in diabetics. These patients may be more prone to perioperative hypotension, bradycardia, and hypoglycemia.

**Prophylaxis And Treatment Of Postoperative Myocardial Ischemia:**

**Beta Blockers.** Beta adrenergic blocking drugs, through their ability to suppress perioperative tachycardia, appear most efficacious in preventing perioperative myocardial ischemia. They are well tolerated by most surgical patients and may reduce long-term cardiac events. Beta adrenergic blocking drugs have been approved for treatment of hypertension, supraventricular tachycardias, ventricular arrhythmias, angina, and myocardial infarction. They are a cornerstone of chronic post-MI therapy, as they reduce subsequent reinfarction. Antihypertensive effects of beta blockers are useful during adrenergic activation during events such as endotracheal intubation, extubation, ECT, and sternotomy. They also blunt tachycardia at these times, and this is likely the predominant mechanism of their antiischemic effects. Several trials which document the ability of beta blockers to improve perioperative cardiac outcomes have been

published, though several very recent trials have questioned this conclusion. Recent work suggests that beta blockade is most efficacious in patients with many clinical risk factors and/or positive stress tests. The outcome benefit from perioperative blockade may persist for up to two years after vascular surgery in high-risk patients. Beta1 selective drugs are less likely to cause bronchospasm, even in patients with reactive airway disease. Still, asthma and COPD are relatively contraindications to beta blockade. There is a very small subset of patients with severe coronary artery disease (floridly positive stress tests in multi-vessel distributions) who appear not to benefit from beta blockade; such patients may be considered candidates for myocardial revascularization. Two recent trials (MAVS, DIPOM) have questioned the perioperative protective effects of beta blockade; the large POISE trial, when it is completed, should provide further guidance.

Other anti-anginal drugs appear less promising. Two studies, one in nocardiac surgery, and one in fast-track CABG surgery, have found that prophylactic intravenous nitroglycerin failed to reduce the prevalence of perioperative myocardial ischemia or infarction. This may have been due to compensatory increases in heart rate. The short-acting calcium antagonist nifedipine may increase mortality after acute MI and should probably not be used as a first line drug for acute control of hypertension in patients with CAD.

**High Dose Narcotics / Prolonged Anesthesia.** High-dose sufentanil anesthesia may reduce the stress response and improve overall outcome after abdominal aortic surgery. The McSPI group showed that postoperative infusion of sufentanil 1 mcg/kg/hr reduced myocardial ischemia following CABG. This approach, however, mandates overnight ventilation, which may not be a cost-effective therapy. The value of propofol, remifentanil, dexmedetomidine, or infusions of other short-acting intravenous agents in maintaining postoperative cardiovascular homeostasis remains unclear. A small trial has suggested that a propofol-based general anesthetic for carotid endarterectomy is associated with less myocardial ischemia than is an isoflurane-based technique.

**Epidural Analgesia.** Epidural anesthetics reduce cardiac preload and afterload, postoperative adrenergic and coagulation responses, and produce coronary vasodilatation (thoracic epidurals only). These effects suggest that they may reduce perioperative myocardial ischemia. However, evidence of benefits in cardiac outcome has been limited in individual trials. Concerns about respiratory depression, neuroaxis hematomas, and the expense of surveillance have limited the use of epidural narcotics in greater numbers of patients. Epidural anesthesia may improve other organ system outcome, but its ability to reduce myocardial infarction remains speculative. Providing aggressive postoperative analgesia may be labor-intensive, and the cost-effectiveness remains unclear at this time. Two recent meta-analyses suggest that regional anesthesia may indeed be associated with a one-third reduction in perioperative myocardial infarction, especially if spinals or thoracic epidurals are used.

**Volatile Anesthetics.** Volatile anesthetics reduce myocardial infarct size. The preconditioning effects of volatile anesthetics suggest that they should be incorporated into general anesthetic techniques for patients with known or suspected coronary artery disease.

**Non-steroidal anti-inflammatory drugs (NSAIDs)** might be particularly useful in surgical patients with coronary artery disease due to their analgesic and antiplatelet effects, but substantial data is lacking. Ketorolac may reduce the stress response to surgery without increasing bleeding times or producing renal insufficiency. A randomized trial has demonstrated that the addition of ketorolac to morphine PCA can reduce the prevalence of myocardial ischemia following total joint arthroplasty. Whether this is due to improved analgesia or anti-platelet effects is not clear at this time. However, concerns about increased postoperative hemorrhage make the use of these therapies in surgical patients controversial. A decision analysis has suggested that the benefits of aspirin in vascular surgery patients exceed the risks. COX-2 inhibitors are effective analgesics in the perioperative period. However, their chronic use does not protect the heart as much as do NSAIDs with direct platelet actions, and they may impair preconditioning. Their use appears contraindicated in cardiac surgery, and possibly in vascular surgery.

**Alpha2 Agonists.** Alpha2 adrenergic receptors at presynaptic terminals mediate a reduction in norepinephrine release from presynaptic terminals, thereby decreasing noradrenergic central nervous system transmission and producing sedation, anxiolysis, and analgesia. Clonidine premedication reduces hypertension, tachycardia, and norepinephrine levels in patients undergoing aortic reconstruction. Clonidine also suppresses the normal postoperative increase in fibrinogen levels and antagonizes epinephrine-induced platelet aggregation. Our work has shown that clonidine can reduce intraoperative myocardial ischemia. The more specific alpha2 agonists dexmedetomidine and mivazerol may also reduce postoperative myocardial ischemia.

**Statins.** These drugs reduce cholesterol and reduce reinfarction in patients with coronary disease. They can reduce coronary calcium, which may be a predictor of perioperative cardiac events in vascular surgery patients. Several large observation studies and a more recent randomized trial have correlated statin use with reduced rates of perioperative death and long-term postoperative cardiac events.

**Hyperglycemia.** Hyperglycemia appears to impair preconditioning mechanisms. It has been shown to be associated with worse outcomes in surgical ICU patients and after acute myocardial infarction in nonsurgical patients. Impaired insulin sensitivity is common in patients with known or suspected coronary disease and is associated with endothelial dysfunction. While perioperative data is less conclusive, it is likely that tight control of perioperative glucose levels will assume greater importance in the care of these patients in the future.

**Anemia / Hypothermia.** Anemia is associated with an increased prevalence of postoperative myocardial ischemia. Whether more aggressive transfusion lowers this risk is unclear. In high-risk patients and in those who demonstrate myocardial ischemia, we are more likely to transfuse PRBCs to augment hematocrit to 30%. The elusive goal of a blood substitute would allow safer augmentation of oxygen carrying capacity in the future. Hypothermia is also associated with postoperative myocardial ischemia; aggressive warming and heat conservation are warranted during and after surgery in high-risk patients, given recent data suggesting decreased cardiac morbidity when forced-air warming is used in elderly patients.

**Managing Acute MI.** A cardiologist should see patients with suspected MI as soon as possible. Acute care for myocardial infarction includes prompt reperfusion (angioplasty or CABG, since thrombolysis is generally contraindicated after surgery), therapy with aspirin and beta blockers in those who can tolerate them, the avoidance of calcium entry blockers, and the use of ACE inhibitors in those with poor LV function. It is not known if these recommendations are necessarily transferable to the perioperative setting. In patients with evolving myocardial infarction, intraaortic balloon pumping (IABP) can improve coronary blood flow while decreasing workload. Anecdotal reports exist of IABP placement as prophylaxis against postoperative coronary events for NCS, but definitive studies are lacking. IABP use may be particularly risky in patients with peripheral vascular disease.

### **The Future:**

Improvements in our management of these patients appear to be reducing perioperative cardiac morbidity to the point where other organ system dysfunction may be responsible for the majority of in-hospital deaths. If this is true, then we are truly making remarkable strides.

At present, there are rapid changes in the understanding of the pathogenesis of coronary artery disease. This may lead to more widespread primary and secondary prevention (cholesterol reduction, reduction of inflammation) and more aggressive and better revascularization (PTCA/stents). These factors might reduce perioperative cardiac complications. Indeed, in the CARP trial, there were no differences in survival of vascular surgery patients with CAD, whether they were randomized to receive coronary revascularization or not before vascular surgery. In both groups, the majority of patients received beta blockers, aspirin, and statins before surgery. Additionally, given improved medical and revascularization therapy, patients previously considered “too sick” for surgery will present to our ORs (for outpatient procedures, no less!) Future improvements in preventing cardiac deterioration after noncardiac surgery may also involve modulation of the adrenergic response (alpha2 agonists, intensive analgesia) and the coagulation system. The key will be to identify cost-effective strategies that improve outcome and to identify patients most likely to benefit.

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