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Circulation 2009;119;2936-2944
DOI: 10.1161/CIRCULATIONAHA.108.828228
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

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More than 230 million major surgeries are performed annually worldwide,[1] and this number grows continuously. The 30-day mortality associated with moderate- to high-risk noncardiac surgery in recent large cohorts and population-based studies exceeds 2%[2–4] and surpasses 5% in patients at high cardiac risk.[5] Cardiac complications constitute the most common cause of postoperative morbidity and mortality,[4,6] having considerable impact on the length and cost of hospitalization.[7] As our population ages, more high-risk cardiac patients will undergo surgery, and perioperative myocardial infarction (PMI) can be an increasing problem.

Redefinition of PMI

Traditionally, MI was defined by the World Health Organization criteria, ECG criteria, and cardiac enzymes. Defining PMI, however, is often difficult because most PMIs occur without symptoms in anesthetized or sedated patients, ECG changes are subtle and/or transient, and the creatine kinase-MB isoenzyme has limited sensitivity and specificity because of coexisting skeletal muscle injury.[8] Consequently, PMI was often recognized late (postoperative day 3 to 5), resulting in high (30% to 70%[9]) mortality.

Cardiac troponin assays have changed this definition.[10] The recent universal definition of MI[11] is based on a rise and/or fall of cardiac biomarkers (preferably troponin) in the setting of myocardial ischemia: cardiac symptoms, ECG changes, or imaging findings. Studies using serial troponin measurements demonstrate that most PMIs start within 24 to 48 hours of surgery during the greatest postoperative stress.[12–15] Le Manach et al[15] observed early (<24 hours) and late (>24 hours) peaks in troponin in 1136 patients after abdominal aortic aneurysmectomy. Yet, 90% of troponin elevations began within <24 hours.

Pathophysiology

Two distinct mechanisms may lead to PMI: acute coronary syndrome and prolonged myocardial oxygen supply-demand imbalance in the presence of stable coronary artery disease (CAD), designated type 1 and type 2 by the universal definition of MI.[11] This distinction is key to therapeutic considerations.

Acute Coronary Syndrome (Type 1 PMI)

Acute coronary syndrome occurs when an unstable or vulnerable plaque undergoes spontaneous rupture, fissuring, or erosion, leading to acute coronary thrombosis, ischemia, and infarction. Although it is currently widely accepted that intraplaque inflammation plays a pivotal role in plaque instability and spontaneous acute coronary syndrome,[16] external stressors such as those occurring postoperatively are believed to contribute (Figure 1):

- Physiological and emotional stresses are known to predispose to MI, likely because of the sympathetic induced hemodynamic, coronary vasoconstrictive, and prothrombotic forces thought to promote plaque disruption. These conditions are common perioperatively. Catecholamines and cortisol increase after surgery[17] and may remain elevated for days.[18] Stress hormones increase with pain, surgical trauma, anemia, and hypothermia.[19,20] Plasma catecholamines correlated with postoperative cardiac troponin elevations[19] and with graft occlusion after vascular surgery.[21] Yet, whether they were the cause or the result of these vascular events is unclear.
- Tachycardia and hypertension, common in the perioperative period, may exert shear stress, leading to rupture of plaques with outward (positive) remodeling, thin fibrous caps, and high circumferential tensile stress or to endothelial stripping/erosion caused by high blood velocities around plaques with inward (negative) remodeling and severe coronary stenosis.[22]
- Increased postoperative procoagulants (fibrinogen, factor VIII coagulant, von Willebrand factor, α1-antitrypsin), increased platelet reactivity,[23] decreased endogenous anticoagulants (protein C, antithrombin III, α2-macroglobulin),[24] and decreased fibrinolysis[25] have been reported. However, postoperative hypercoagulability is notorious for its venous complications precipitated by stasis and immobilization, and reports of hypercoagulability and/or decreased fibrinolysis causing

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(*Circulation*. 2009;119:2936-2944.)

Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.108.828228

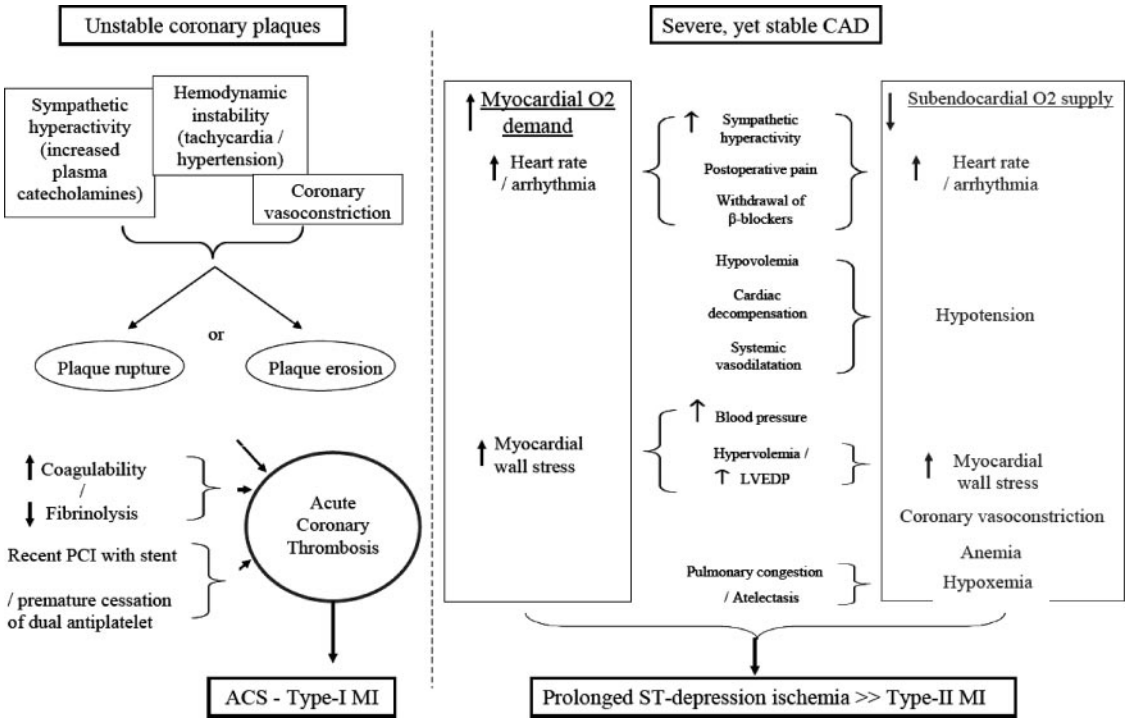

Figure 1. The 2 distinct mechanisms of PMI.

myocardial ischemia,[26,27] infarction,[28] or arterial bypass thrombosis[29] are scarce.

Myocardial Oxygen Supply-Demand Imbalance (Type 2 PMI)

Numerous studies[30] using perioperative Holter monitoring in high-cardiac-risk patients undergoing major surgery showed that silent, heart rate–related ST-segment depression is common postoperatively and is associated with in-hospital[22,31] and long-term morbidity and mortality.[32] Postoperative cardiac complications, including sudden death,[33,34] occurred after prolonged (>30 minutes,[35,36] >2 hours,[37,38] or >5 hours[39,40]) silent ST-segment depression. These findings were further corroborated by studies that correlated continuous, online 12-lead ST-segment analysis with serial cardiac troponin measurements after major vascular surgery.[12,41] Cardiac troponin elevations occurred after prolonged (226±164 minutes), transient, postoperative ST-segment depression (Figure 2), and peak troponin elevations correlated with the duration of ST depression.[12] ST elevation occurred in <2% of postoperative ischemic events and was a rare cause of PMI.[12,30,41] Hence, prolonged, ST-depression–type ischemia is the most common cause of PMI.

Furthermore, studies using current highly sensitive troponin essays showed that low-level, yet prognostically significant, troponin elevations are common in high-cardiac-risk patients postoperatively even with little or no evidence of ECG ischemia.[41,42] Troponin T elevations above the low cutoff level (>0.03 ng/mL) occurred in 24% of patients early after vascular surgery, only 32% of whom had ECG ischemia, whereas among 8.7% patients with PMI (troponin T >0.1 ng/mL), 88% had ischemia on continuous 12-lead ECG monitoring.[41] Higher troponin values correlated with longer ST depression and more pulmonary congestion or chest pain.[12] Thus, prolonged postoperative ischemia, myocardial injury, and type 2 PMI span a spectrum from silent, minor injury with low-level troponin elevations and low frequencies of ECG ischemia to prolonged, overt ischemia in multiple ECG leads, marked troponin elevation, and PMI (Figure 2). Although troponin elevation is common mainly among patients with history of CAD[41–44] or moderate to severe ischemia on preoperative stress thallium scanning,[45] troponin elevations occur also in the setting of septic shock, renal failure, or pulmonary embolism.[46] These causes, however, are less frequent and occur later after surgery than PMI.

Tachycardia is the most common cause of postoperative oxygen supply-demand imbalance.[12,47] Heart rates >80 or 90 bpm in patients with significant CAD whose preoperative resting heart rate is 50 to 60 bpm can lead to prolonged ischemia and PMI (Figure 2), demonstrating the low threshold for ischemia after surgery. Postoperative hypotension (hypovolemia, bleeding, or systemic vasodilatation), hypertension (elevated stress hormones, vasoconstriction), anemia,[48] hypoxemia, and hypercarbia aggravate ischemia. Stress-induced and ischemia-induced coronary vasoconstriction[49] further impairs coronary perfusion. Furthermore, systolic and/or diastolic dysfunction common in patients with CAD is aggravated by ischemia and volume overload, leading to cardiac decompensation and type 2 PMI (Figure 3).[50]

Angiographic and Pathological Studies

Ellis et al[51] examined 1242 patients who underwent routine coronary angiography before major vascular surgery as part of a practice common in the Cleveland Clinic at the time to perform preoperative coronary revascularization in patients with evidence of severe CAD. They found that 17 of 21

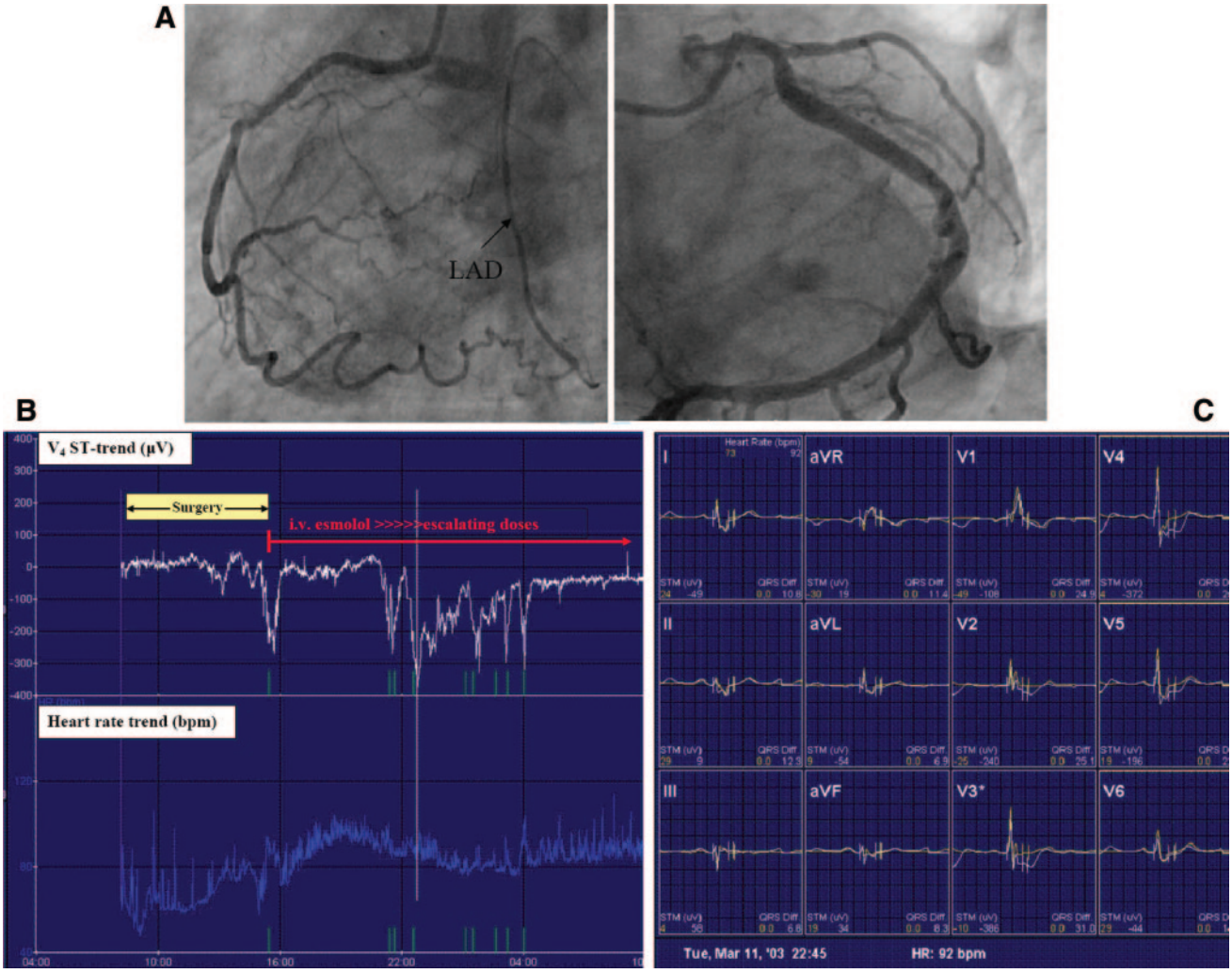

Figure 2. A 67-year-old man underwent abdominal aortic aneurysm repair. Because of severe ischemia on preoperative dipyridamole-thallium scanning, the patient underwent coronary angiography (A) that showed total ostial occlusion of the LAD with retrograde filling through the RCA and no additional significant CAD. An echocardiogram showed normal size and function of both ventricles and moderate mitral incompetence. After pretreatment with prophylactic bisoprolol 5 mg QID for a month before surgery in addition to his long-term medications (enalapril, simvastatin, and aspirin), the patient was admitted to surgery. His intraoperative course was uneventful. His heart rate during the operation was 50 to 65 bpm. Immediately after surgery, the patient's heart rate increased to 92 bpm, and deep ST depressions were noted in leads V_2 through V_5 on a continuous, online 12-lead ECG (B). Immediate treatment with intravenous esmolol and labetalol slowed his heart rate and reversed the ischemic ECG changes. Esmolol infusion was continued. Nevertheless, 5 hours later, another episode of severe ischemia occurred in leads V_2 through V_5 at a heart rate of $<$100 bpm (B, C). ST-depression ischemia in the precordial leads (maximal in V_3 and V_4) waxed and waned for almost 7 hours. An echocardiogram showed significant hypokinesia of the anterior wall. A chest x-ray showed pulmonary congestion. The tachycardia and ischemia resolved slowly with the combination of intravenous esmolol, phenylephrine, slow infusion of packed red blood cells, and furosemide. Troponin T increased to a peak of 0.67 ng/mL on the day after surgery and gradually returned to normal 5 days later.

patients (81%) with PMI or cardiac death also had chronic total coronary occlusions with collaterals on preoperative coronary angiography as opposed to only 29% of 42 matched control patients without cardiac complications. Patients with PMI or cardiac death had more coronary vessels with critical ($\geq$70%) stenosis (2.1$\pm$1.4 versus 0.7$\pm$1.2, respectively).

Two small, retrospective autopsy studies investigated coronary anatomy in patients with fatal PMI. Dawood et al[52] found plaque rupture in 7% and thrombus in 28% of 42 autopsied patients. Problems such as the timing of autopsies relative to PMI obviously limited the ability to estimate the true prevalence of coronary arterial thrombotic events in such patients. In contrast, intraplaque hemorrhage without plaque disruption, noted in 45% of their patients, is a common finding in advanced CAD that does not indicate the cause of cardiac death.[53] Cohen and Aretz[54] studied 26 patients who died of PMI. Only 12 (46%) had plaque rupture. Interestingly, most patients (71%) without plaque rupture died within 3 days of surgery (median, 2 days), whereas those with plaque rupture died at random distribution within 3 weeks from surgery (median, 7 days) without a clear relationship to the time of surgery.

Prognosis

Early mortality after PMI ranges from 3.5% to 25%[13,15,31,41,42,55] and is higher among patients with marked troponin elevation compared with patients with minor troponin elevation (0% to

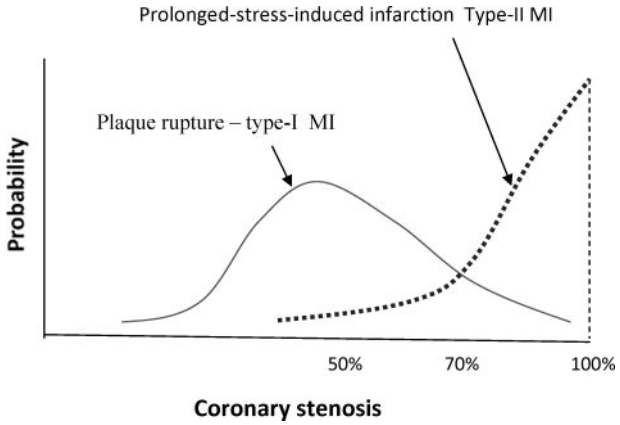

Figure 3. The probability of type 1 and 2 MI as a function of the severity of CAD. Adapted from Landesberg G. The pathophysiology of perioperative myocardial infarction: facts and perspectives. *J Cardiothorac Vasc Anesth*. 2003;17:90–100,[50] copyright © 2003, with permission from Elsevier.

7%).[15,41,42] PMI also affects long-term survival.[56] Even low-level troponin elevation predicts increased long-term mortality, and higher postoperative troponin values predict worse survival[41,42,57] (Figure 4).

Prevention and Treatment

Prophylactic Therapy

β-Adrenergic Blockers

Prophylactic β-blockade has been advocated on the basis of 2 small randomized trials that showed reduced perioperative and long-term MI and death.[58,59] Four subsequent trials[6,60–62] using different dosages and types of β-blockers failed to reproduce these benefits. The large Perioperative Ischemic Evaluation (POISE) trial[6] (8351 patients) reported increased mortality (by 31%) and stroke (by 100%), mostly in association with hypotension and bleeding, in patients treated with metoprolol despite a reduction in nonfatal PMI by 26%. In meta-analyses, trials achieving the most effective heart rate control were associated with less PMI.[53] However, β-blockade did not reliably decrease heart rate and was associated with more adverse events.[63,64] β-Blockade may aggravate hypotension (12% of POISE patients) and interfere with the ability to maintain adequate cardiac output during active bleeding, anemia, or infection.[65] Consequently, the use of β-blockade as prophylaxis is currently strongly debated.[66] The consensus is that long-term β-blockade should not be discontinued.[67] Intravenous β-blockers are often used to treat tachycardia, hypertension, or ischemia with results comparable to or better than those reported with prophylactic β-blockade.[68] No study has compared prophylactic β-blockade with short-term, clinically indicated postoperative use.

Calcium-Channel Blockers

None of the randomized trials has shown reduced PMI or death, despite less supraventricular arrhythmia and ischemia in thoracic surgery.[69] A meta-analysis of 11 trials found reduced combined perioperative death or PMI by posthoc analysis but more hypotension with calcium channel blockers.[68]

α2 Agonists

Only 1 randomized controlled trial reported reduced PMI and death in 904 major vascular surgery patients treated with mivazerol but not in other patients.[70] However, mivazerol is unavailable for clinical use. Other trials using prophylactic clonidine or dexmedetomidine reported no benefit,[71] except for 1 small study that suggested reduced perioperative ischemia and 2-year mortality with perioperative transdermal clonidine.[72]

Statins

HMG-CoA reductase inhibitors should be continued perioperatively with the presumption that abrupt withdrawal may

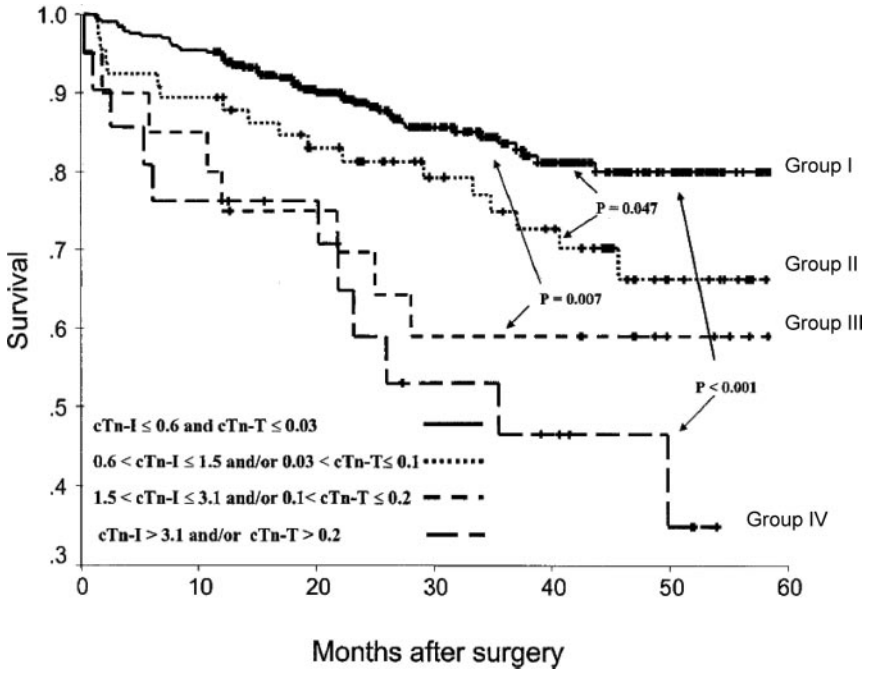

Figure 4. Long-term survival of patients after major vascular surgery divided according to their highest troponin elevation obtained in the first 3 after days. Adapted from Landesberg G, et al. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. *J Am Coll Cardiol*. 2003;42:1547–1554),[41] copyright © 2003, with permission from the American College of Cardiology.

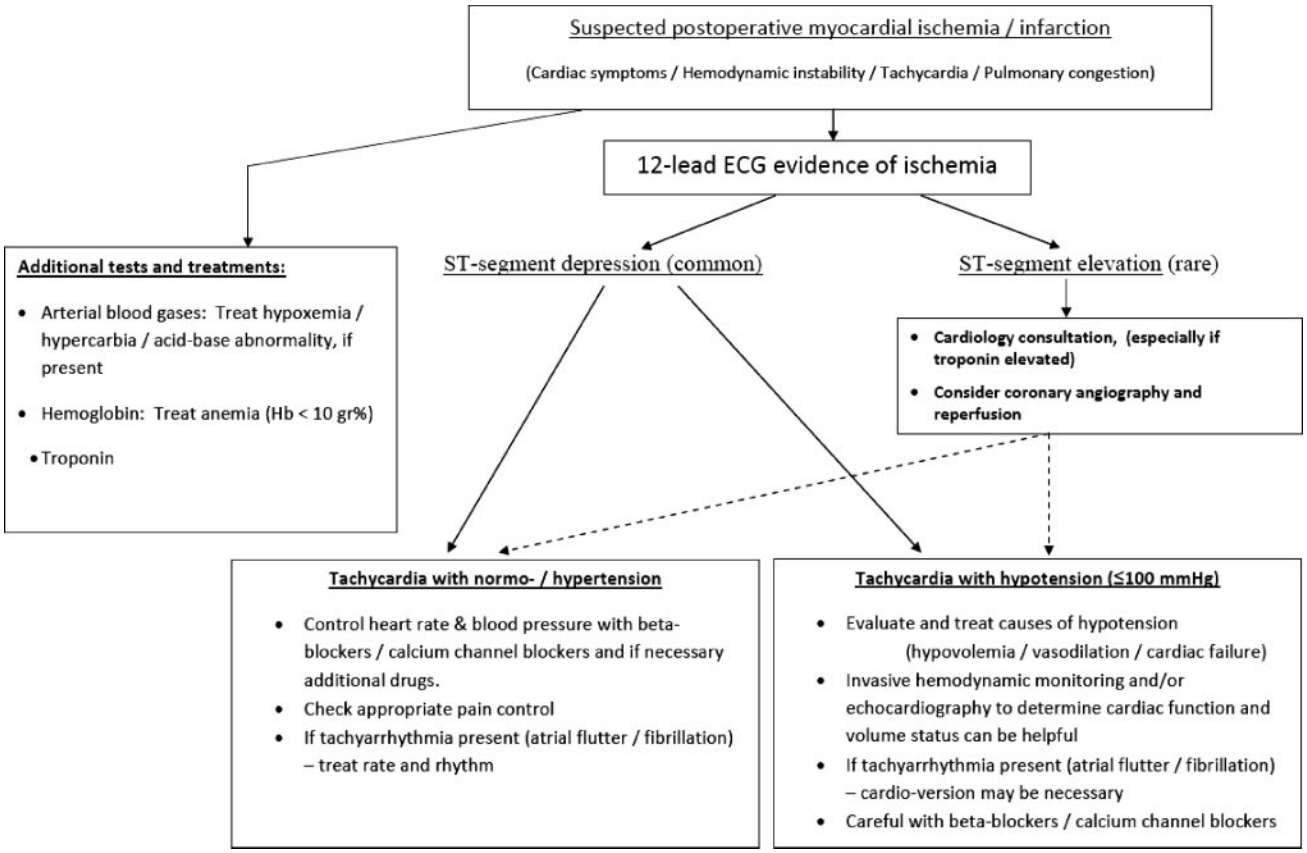

Figure 5. Treatment and prevention of postoperative myocardial ischemia and MI.

cause plaque destabilization.[73] Several studies, most retrospective, have reported reduced perioperative and long-term cardiac complications with statins.[74–78] Currently, 2 trials[79,80] (total, 600 patients; 1 is in abstract form) have shown a >50% reduction in PMI and mortality. Larger randomized controlled trials are still needed.

Aspirin

It is accepted practice to discontinue aspirin 5 to 7 days before a surgical procedure to prevent bleeding, although recent analyses suggest that there is only a mild increase in the frequency of bleeding with aspirin and no increase in its severity or mortality.[81,82] Possible exceptions are intracranial and prostate surgery. Conversely, however, the effectiveness of continuing aspirin has been suggested only in coronary artery bypass graft surgery,[83] not in noncardiac surgery.[84]

Dual Antiplatelet Therapy

Patients receiving dual antiplatelet therapy (usually clopidogrel and aspirin) after recent coronary stent implantation are at increased risk for acute stent thrombosis (type 4b MI[11]) if antiplatelet therapy is discontinued prematurely but also at increased risk of bleeding if these medications are continued perioperatively.[85] Current guidelines mandate dual antiplatelet therapy for at least 4 weeks after bare metal stent implantation and for at least a year after drug-eluting coronary stenting. Elective surgery during this period is discouraged. Several studies have reported an inverse relationship between the time after PCI and perioperative major adverse cardiac events.[86] For bare metal stenting, the incidence of in-hospital major adverse cardiac events decreases from 10.5% at <30 days to 2.8% at >90 days.[87] For drug-eluting coronary stenting, the risk of perioperative MACE is stable (5.9% to 6.4%) during the first year and declines to 3.3% thereafter.[88] If discontinuation of thienopyridine is necessary, continuing aspirin and restarting the thienopyridine as soon as possible after surgery is prudent. "Bridging" stent patients with antithrombin, anticoagulants, or glycoprotein IIb/IIIa agents has not been proven effective.

Coronary Revascularization

Prophylactic preoperative coronary revascularization, mostly by coronary artery bypass graft surgery, was associated with improved outcomes in 8 studies (6 retrospective) including >10 000 patients undergoing major vascular surgery.[89] Two recent prospective randomized trials (Coronary Artery Revascularization Prophylaxis [CARP][90] and Dutch Echographic Cardiac Risk Evaluation Applying Stress Echo [DECREASE]-V[91]; total, 611 patients) failed to show such benefit. However, 59% to 65% of randomized patients in those trials were treated with PCI, which provides less complete revascularization, is associated with more perioperative complications, and has questionable efficacy for improving survival in stable CAD.[92] In a reanalysis of CARP, coronary artery bypass graft surgery and complete revascularization were associated with significantly less PMI.[93] Until further data are available, prophylactic preoperative coronary revascularization is currently rarely recommended.

Perioperative Management

Martinez et al[94] have recently presented results of a randomized trial involving 316 major vascular surgery patients. Among 80 patients with prolonged (≥20 minutes) ischemia on continuous online 12-lead ECG monitoring, β-blockers and optimization of myocardial oxygen supply-demand balance lowered 6-month mortality (8% versus 20%,) and reduced troponin values.

The importance of preventing even modest increases in heart rate cannot be overemphasized. All causes of tachycardia, hypertension, hypotension, anemia, and pain should be treated aggressively. Treatment of tachycardia associated with hypotension is particularly challenging and requires an understanding of the patient's baseline and postoperative myocardial, valvular, and coronary physiology. Frequently, vasopressors to maintain blood pressure and β-blockers to slow heart rate while managing blood volume, postoperative pain, and respiratory function are necessary. Emergent coronary intervention, anticoagulants, or glycoprotein IIb/IIIa antagonists are rarely indicated in the immediate postoperative course and are hazardous because of the risk of bleeding, unless ST elevation or intractable cardiogenic shock ensues[95] (Figure 5).

Anemia (hematocrit <39%) independently predicts 30-day mortality, and its correction improved survival in 1 cohort of noncardiac surgery patients.[96] Blood transfusion improved survival in critically ill patients with CAD and hemoglobin <10% but not in nonischemic patients.[97] Other studies reported increased mortality and nosocomial infections with blood transfusion for hematocrit >25% in stable patients with acute coronary syndrome,[98] in patients after cardiac surgery,[99] and in intensive care patients.[100] Therefore, hematocrit between 25% and 33% is a gray zone in which transfusion must be individualized. Hemodynamically unstable postoperative patients with ischemia may benefit from transfusion. Tight perioperative hemodynamic monitoring, including echocardiography, arterial line, central venous, or possibly pulmonary arterial pressure measurement, is often necessary to determine volume status and to avoid congestive failure. Multilead ECG monitoring to detect silent myocardial ischemia is also recommended (Figure 5).

Conclusions

Postoperative tachycardia, hypotension, hypertension, anemia, hypoxemia, and systolic and diastolic myocardial dysfunction are common causes of prolonged ST-depression and type 2 infarction in patients with stable CAD undergoing major noncardiac surgery. Although the incidence of type 1 PMI cannot be determined with confidence from available data, the weight of evidence, mainly the rare occurrence of ST-elevation MI, suggests that it is much lower than that of type 2 PMI. PMI is often silent and its ECG changes are frequently transient, yet even minor troponin elevations predict early and late morbidity and mortality. Many questions relating to perioperative pharmacological therapy to prevent PMI remain unanswered. Careful perioperative monitoring for ischemia, a low threshold for treating and preventing tachycardia while avoiding hypotension, decreased cardiac output, and/or cardiac decompensation help prevent PMI. Coronary intervention is rarely indicated as the first line of treatment, and antithrombotic therapy may exacerbate bleeding. Future studies are needed to determine which patients with PMI require intensified postoperative surveillance, medical therapy, and/or coronary intervention to improve long-term survival.

Disclosures

Dr Jaffe is or has been a consultant to most of the major diagnostic companies manufacturing troponin assays. He also consults for Merck and GSK.

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KEY WORDS: myocardial infarction ■ general surgery ■ surgery