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How to prevent perioperative myocardial injury: The conundrum continues

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Abstract

Background

Perioperative myocardial injury (PMI) remains a major cause of perioperative morbidity and mortality but clinical strategies to prevent PMI are still uncertain.

Methods and Results

We comprehensively searched PubMed for major research articles concerning clinical strategies to prevent PMI. The key findings are as follows: (1) the American College of Cardiology/American Heart Association guideline update for perioperative cardiovascular evaluation for noncardiac surgery is very useful to stratify cardiac risk preoperatively; (2) cardiac troponin has emerged as a biomarker to diagnose postoperative PMI and to predict clinical outcomes; (3) coronary revascularization before noncardiac surgery probably would provide cardiac protection in select patients, especially in patients with high-risk coronary artery disease; (4) elective noncardiac surgery should be postponed in patients who received coronary stenting recently because of high incidence of serious cardiac complications (minimum 68 weeks for bare metal stents and 6-12 months for drug-eluting stents); and (5) β -blockers and statins are very promising drugs and probably would prevent PMI in a select patient population, especially in patients with intermediate risk and stable coronary artery disease.

Conclusions

Further studies, especially randomized clinical trials and mechanistic investigation are

needed to find the best and effective clinical strategies to prevent/reduce PMI. (Am Heart J 2007;154:1021-8.)

Perioperative myocardial injury (PMI), including myocardial ischemia, cardiac dysfunction, cardiac arrhythmias, myocardial infarction, and cardiac arrest continues to be a major challenge to perioperative physicians because its incidence has not substantially decreased for the past 2 decades.^{1,2} Despite extensive clinical and basic research, the mechanisms responsible for PMI remain enigmatic. Currently, the predominant theories are that PMI may be caused by prolonged stress-induced myocardial ischemia, atherosclerotic plaque rupture, or a combination of the two. Clinically, perioperative myocardial ischemia and infarction may present differently; pathologically, they are all secondary to alterations of coronary plaque morphology and function and/or the loss of balance between myocardial oxygen supply and demand, in which inflammation has been linked with the development of atherosclerotic disease and instability and may cause acute coronary syndromes (ACSs) and PMI.

The potential triggers for PMI include surgical stress, catecholamine release, and inflammatory reaction; prolonged/repeated stress or extreme surgical stress especially may inflict inflammation and induce repeated/prolonged myocardial ischemia, which may serve as a primary cause for PMI, including perioperative myocardial infarction. Several lines of evidence support this hypothesis. First, perioperative cardiac complications are preceded almost universally by long-rather than short-duration ST-segment changes—an indication of pro-longed myocardial ischemia.^{3,4} Second, most perioperative myocardial infarctions occur early after surgery (most stressful time) and are asymptomatic (“silent” myocardial infarction)^{5,6}; most of them are preceded by episodes of increases in heart rate^{4,6} and show non-Q wave rather than Q wave myocardial infarction,^{3,5} whereas clinical studies have well demonstrated that complete coronary occlusion is infrequently observed in patients with non-Q wave myocardial infarction (only 26%-42%) compared with patients with Q wave infarction ($\geq 84\%$).⁷ Third, β -adrenergic receptor blockers, because of their inherent role of blocking sympathetic activation, have been shown to reduce perioperative ischemia and the risk of myocardial infarction and death in high-risk surgical patients (see below). Finally, our recent study demonstrated that chronic catecholamine stimulation can aggravate myocardial injury by provoking inflammatory reaction and increasing myocardial apoptosis, thereby illustrating a mechanistic link between extreme/prolonged surgical stress \rightarrow catecholamine release \rightarrow inflammation/myocardial apoptosis and PMI.⁸

Nevertheless, coronary plaque disruption was found in more than half of fatal perioperative myocardial infarctions and was considered as a primary cause of fatal

perioperative myocardial infarction.^{9,10} More likely, surgery, especially major surgery with its associated trauma, anesthesia, pain, bleeding, and hypothermia, is comparable to an extreme stress test, thereby producing a triggering/provoking effect in the pathogenesis of PMI (ie, inflicting inflammation and destabilizing plaques) and ultimately leading to appearance of PMI.

Clinical strategies to prevent PMI have been evolving greatly. In 1977, Goldman et al¹¹ pioneered the concept of a risk index to account for the multifactorial nature of contributors to risk of cardiac morbidity, which has led to the landmark development in perioperative medicine, that is, the American College of Cardiology (ACC)/ American Heart Association (AHA) guidelines for perioperative cardiovascular evaluation for noncardiac surgery in 1996¹² and an update in 2002.¹³ These guidelines focused on preoperative testing to identify patients with significant coronary artery disease (CAD) and subsequent coronary revascularization in select patients. The guidelines currently play a major role in perioperative medicine. However, because of the poor positive predictive value of noninvasive cardiac stress tests, the controversy about the benefit of coronary revascularization before noncardiac surgery, and the considerable risk of coronary angiography and coronary revascularization in high-risk patients, perioperative physicians have been continuously searching for alternative approaches to prevent/reduce perioperative cardiac complications. In 1996, Mangano et al¹⁴ performed a randomized clinical trial (RCT) to investigate the effect of the β -blocker, atenolol, on patient outcomes and concluded that in patients with risk for CAD who must undergo noncardiac surgery, treatment with atenolol during hospitalization can reduce mortality and the incidence of cardiovascular complications for as long as 2 years after surgery. In 2003, Poldermans et al¹⁵ provided evidence in a case-controlled study that statin use reduces perioperative mortality in patients undergoing major vascular surgery. More recently, the ACC/ AHA updated their recommendations on perioperative β blocker therapy.¹⁶ These significant developments in perioperative medical therapy to prevent/reduce PMI have shifted the interest in perioperative cardiac care greatly, from risk stratification and potential coronary revascularization to risk modification with β -blockers and/or statins. Nevertheless, the debate and controversy exist in almost every aspect of clinical strategies to prevent PMI. These strategies include mainly preoperative cardiac risk assessment, perioperative monitoring, prophylactic coronary revascularization, coronary stents, and perioperative medical therapy.

Preoperative cardiac risk assessment

The ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery can help to stratify cardiac risk and identify the patients who need preoperative interventions to reduce cardiac risk.¹³ The rationale for intensive screening is based on the assumption that coronary revascularization prevents PMI in patients with CAD. As the ACC/AHA task force stated in the guideline: “A large proportion of the data

used to develop these guidelines are based on observational or retrospective studies or knowledge of management of cardiovascular disorders in the nonoperative setting. Although the collective body of knowledge about the identification of high- and low-risk patients by perioperative clinical and noninvasive evaluation is substantial, the number of prospective or randomized studies that have been performed to establish the value of different treatments on perioperative outcomes is small.”¹³ Based on the guidelines, many patients undergo preoperative testing for detection of CAD before noncardiac surgery. However, noninvasive cardiac stress testing for perioperative myocardial infarction or death has very poor positive predictive values (b20%), although it has excellent negative predictive values (near 100%).¹⁷ Therefore, there is uncertainty and much debate on how to prepare surgery for the patient who has positive results from preoperative cardiac stress testing, that is, medical therapy versus coronary revascularization. In addition, very few RCTs support either of the treatments (see below).

The Lee et al¹⁸ revised cardiac risk index is a simple and practical clinical risk index. It includes 6 variables to identify patients at high risk for perioperative cardiac complications: history of CAD, history of congestive heart failure, history of cerebral vascular accident, preoperative insulin treatment, serum creatinine level ≥ 2.0 mg/dL, and high-risk surgical procedure. The presence of 3 or more of these risk variables (class III and IV) conferred an event rate as high as 11% in a group of 1422 patients, whereas the event rate was 1% in the presence of one or none of these variables (class I and II).¹⁸

Other investigators also approached the problem of assessing PMI risk through the development of multivariate models; they proposed that the expected risk from these risk indices may vary along institutions¹⁹ and a test required by these indices should only be performed if this has consequences on perioperative management.¹³ And this is why routine electrocardiogram and chest x-ray have been abandoned as preoperative tests in low- and intermediate-risk surgical patients without specific indications.

Perioperative monitoring

Cardiac troponin I (cTnI) and cTnT have become the biomarkers of choice to diagnose myocardial infarction and to risk-stratify patients with suspected ACS. A recent study by Wong et al²⁰ demonstrated that cTn elevations were associated with a higher risk of multi-vessel disease, complex lesion morphology, and visible thrombus on coronary angiography. Moreover, such patients had more impairment in microvascular function, thereby suggesting a greater propensity for distal embolization of plaque material to the microvasculature. Recently, intravascular ultrasound studies have illustrated that those patients with ACS and elevated troponin levels had greater atheroma burden at the lesion site, more reference segment atherosclerosis, and more frequent findings compatible with

thrombus at the lesion compared with patients who did not have troponin elevation.²¹ Taken together, these findings likely explain the consistent association between troponin elevation, even at low levels, and recurrent ischemic events in patients with ACS.

In surgical patients, Landesberg et al²² and Kim et al²³ have demonstrated that postoperative cTn measurements can detect postoperative myocardial infarction and predict short-term (6 months) and long-term (1-5 years) survival after vascular surgery. Recently, in a study with intense postoperative cTnI surveillance in 1136 patients who underwent abdominal aortic surgery, Le Manach et al²⁴ revealed 2 types of PMI according to the time of appearance and rate of increase in cTnI: acute (b24-hour) and early increases of cTnI above threshold may indicate acute coronary occlusion for early morbidity; prolonged low-level cTnI release followed by a delayed (N24 hours) increase of cTnI may lead to prolonged myocardial ischemia for later events. They proposed monitoring perioperative cTnI concentrations and early institution of treatment for patients with increased cTnI before it leads to irreversible necrosis.

Recently, Mahla et al²⁵ investigated the use of cardiac stress marker, N-terminal pro-brain natriuretic peptide (NT-proBNP), to stratify PMI risk in patients undergoing vascular surgery and found that a single postoperative NT-proBNP determination provides important additional prognostic information for in-hospital and late cardiac events and therefore may support therapeutic decisions to prevent subsequent myocardial damage. This study again provides evidence that the extent of surgical stress is closely related with risk of PMI.

Despite the progress in clinical application of biomarkers for myocardial injury, such as cTn as a marker of myocardial necrosis, there is still a lack of markers of myocardial ischemia, especially the biomarkers that

- (1) can detect myocardial ischemia without myocardial necrosis,
- (2) increase the size of release proportional to the extent of ischemia,
- (3) appear in circulation rapidly after onset of ischemia and last long enough for the detection, and
- (4) are easy to measure with high sensitivity and reasonable specificity.

Prophylactic coronary revascularization

The role of prophylactic/preoperative coronary revascularization in patients with CAD before noncardiac surgery has been examined carefully in several clinical studies but remains controversial. ACC/AHA guidelines update recommended coronary revascularization only for subgroups of high-risk patients with unstable cardiac symptoms or those for whom coronary artery revascularization offers a long-term benefit, independent of the need for noncardiac surgery.¹³ This recommendation was based predominately on the CASS²⁶ as follows.

Coronary artery bypass graft before noncardiac surgery

In 1997, the CASS investigators reported their study, which is the largest study to date and included 3368 noncardiac operations performed within a 10-year period among patients assigned to medical therapy or coronary artery bypass graft (CABG). In this study they found that among 1961 patients undergoing higher risk surgery (involving the thorax, abdomen, vasculature, and head and neck), prior CABG was associated with fewer postoperative deaths (1.7% vs 3.3%, $P = .03$) and myocardial infarctions (0.8% vs 2.7%, $P = .02$) compared with medically managed CAD. There was no difference in the outcome of patients undergoing low-risk procedures such as breast and urologic surgery. They concluded that “in patients with known CAD, noncardiac surgeries involving the thorax, abdomen, vasculature, and head and neck are associated with the highest cardiac risk, which is reduced among patients with prior CABG.”²⁶ However, major limitations of the CASS are that the mortality and morbidity associated with CABG was not factored into the analysis of perioperative outcomes and that perioperative medical treatments, such as perioperative β -blocker and statin therapy, have undergone major improvements since the study was published 10 years ago.

Coronary revascularization before vascular surgery

In the CARP trial, however, McFalls et al²⁷ reported that patients with stable CAD who were scheduled for elective vascular operations at 18 Veterans Affairs hospitals were randomly assigned to undergo coronary revascularization (CABG or percutaneous coronary intervention [PCI]) or medical therapy. After the vascular surgery, there were no differences between the 2 groups in the incidence of myocardial infarction or mortality (a median follow-up of 2.7 years), and therefore coronary revascularization by either CABG or PCI before elective vascular surgery cannot be recommended in patients with stable CAD. This randomized study provided evidence that coronary revascularization in patients with stable CAD does not provide better protection when compared to current medical therapy, which included β -blockers and statins. The study, however, excluded patients with symptoms of unstable coronary disease, left main CAD, aortic stenosis, or severe left ventricular dysfunction, which are class I indications for CABG based on ACC/AHA guidelines for CABG surgery published in 1999.²⁸

In contrast, other studies by Eagle et al,²⁶ Landersberg et al,²⁹ and Garofalo et al³⁰ have shown that previous coronary revascularization provides protection against adverse cardiac events and mortality after vascular surgery. The causes responsible for the difference between the above studies are unclear but probably are due to patient populations included in those studies being different. Taken together, for upcoming surgery, patients with high-risk CAD (left main or 3-vessel disease, poor left ventricular function, and/or diabetes) probably will benefit from coronary revascularization, whereas

patients with intermediate-risk and stable CAD will be more likely to do better with optimal medical therapy.^{13,26-30}

CABG versus PCI (angioplasty or stenting) before vascular surgery

In the substudy of the CARP trial, Ward et al³¹ compared clinical outcomes in patients receiving CABG versus PCI as prophylaxis for elective vascular surgery and found that compared with patients with PCI (131 patients), patients with CABG (91 patients) had fewer myocardial infarctions despite more diseased vessels in the CABG group and tended to spend less time in the hospital after the vascular operation. The authors concluded that more complete revascularization accounted for the intergroup differences.

CABG versus coronary angioplasty before noncardiac surgery

Previous studies have shown that CABG reduces the risk of cardiac complications after noncardiac surgery. Whether coronary angioplasty provides equivalent protection is not known. In BARI, Hassan et al³² found that rates of myocardial infarction and death after noncardiac surgery are similarly low after contemporary bypass surgery or coronary angioplasty in patients with multi-vessel CAD in a randomized study.

Coronary stents in surgical patients

Percutaneous transluminal coronary angioplasty (PTCA) was introduced by Gruntzing in 1977. Sigwart and Puel deployed the first coronary stent in humans in 1986. By 1999, stenting or bare metal stents (BMSs) composed 84.2% of all PCIs.³³ In 2001, the drug-eluting stent (DES) was introduced and 2 years later it was approved by the Food and Drug Administration in the United States.³⁴ At present, most coronary stents have been converted to DES in the United States.³⁴ PTCA, coronary artery stent, and DES are 3 landmark developments in interventional cardiology. However, despite the initial enthusiasm that resulted in the advent of DES, incomplete endothelialization and stent thrombosis continue to plague these devices. Initial studies on animals demonstrated complete endothelialization with BMS at 28 days, whereas DES uniformly showed incomplete healing at 180 days.³⁵

In 2000, Kaluza et al³⁶ first reported on 40 patients treated with BMS who underwent noncardiac surgery within 6 weeks of stent implantation. Seven patients had myocardial infarction, of which 6 were fatal. Other similar studies have also shown a high incidence of cardiovascular complications when noncardiac surgery was performed shortly after coronary stenting or PTCA alone.^{37,38}

The 2007 ACC/AHA for Cardiovascular Angiography and Interventions recommendations for the prevention of stent thrombosis after coronary stent implantation state that, at a minimum, patients should be treated with clopidogrel 75 mg and aspirin 325 mg for 1 month after BMS implantation, 3 months after sirolimus DES implantation, 6 months after paclitaxel DES implantation, and ideally, up to 12 months if they are not at high risk for bleeding.³⁹ This advisory stresses the importance of 12 months of dual antiplatelet therapy after placement of a DES and educating the patient and health care providers about hazards of premature discontinuation. It also recommends postponing elective surgery for 1 year, and if surgery cannot be deferred, considering the continuation of aspirin during the perioperative period in high-risk patients with DES. Nevertheless, in a recent prospective observational study from 3 medical institutions, Vicenzi et al⁴⁰ reported that despite all patients receiving continuous heparin and antiplatelet drugs or only shortly discontinued, nearly half of the patients (46 of 103, 44.7%) who received coronary artery stents within 1 year had complications after surgery; 4.9% of the patients died. All but 2 adverse events (bleeding only) were of a cardiac nature.

At present, for the patients with PCI who require surgery, there is still a lack of consensus regarding how much time should pass between PCI and noncardiac surgery.¹³ However, based on the ACC/ AHA recommendations as above,³⁹ elective noncardiac surgery should be postponed in patients who recently received coronary stenting for a probable minimum of 6 to 8 weeks for BMS and 6 to 12 months for DES. More recently, based on a clinical study in 60 patients, Ingraldi et al proposed that although DES is effective in keeping open diseased heart arteries, they should not be used for patients who need to have noncardiac surgery a short time after an interventional heart procedure; instead, BMS provides a safer choice for these patients (abstract at the 2007 Scientific Session of the Society for Cardiovascular Angiography and Interventions).

Perioperative medical therapy

In recent years, significant progress has been made in medical treatments of cardiovascular diseases. Along with the progress, medical interventions with drugs such as β -blockers and statins have been shown to reduce the occurrence of perioperative cardiac complications, which has brought in the surge of interest on risk modification with medical therapies instead of risk stratification with potential coronary revascularization in surgical patients.

β -Blocker therapy

The ACC/AHA 2006 Guideline Update on Perioperative β -Blocker Therapy¹⁶ is a formal

position statement indicating that performance measures should be limited to class I or class III recommendations—those recommendations in which patients should or should not have the form of therapy—and that they should not include class IIa or IIb recommendations, in which the evidence is less strong and for which opinion dictates the class of indications. Class I recommendation includes the following: (1) β -blockers should be continued in patients undergoing surgery who are receiving β -blockers to treat angina, symptomatic arrhythmias, hypertension, or other ACC/AHA class I guideline indications; (2) β -blockers should be given to patients undergoing vascular surgery at high cardiac risk owing to the finding of ischemia on preoperative testing. Class III recommendation states that β -blockers should not be given to patients undergoing surgery who have absolute contra-indications to β -blockade.

The best protocol for administration of perioperative β -blockers remains uncertain, although previous studies have demonstrated that tight heart rate control by β -blockers^{41,42} reduced perioperative myocardial ischemia and improved clinical outcomes.

Statin therapy

Statin therapy is well established for prevention of cardiovascular disease. Statins may also reduce postoperative mortality and morbidity via a pleiotropic (non–lipid-lowering) effect. Recently, Hindler et al⁴³ conducted a meta-analysis to evaluate the overall effect of preoperative statin therapy on postoperative outcomes. They analyzed the data from 12 retrospective and 3 prospective trials with a total of 223 010 patients and found that preoperative statin therapy was associated with 38% and 59% reduction in the risk of mortality after cardiac and vascular surgery, respectively. When including noncardiac surgery, a 44% reduction in mortality was observed.

Nevertheless, so far there is only one RCT on the effect of statin in patients undergoing noncardiac surgery carried out in Brazil.⁴⁴ In this study with 50 patients in the treatment and 50 in the placebo group, respectively, short-term (45 days) treatment with atorvastatin significantly reduced the incidence of major adverse cardiovascular events after vascular surgery; that is, only 4 cases in the atorvastatin group had adverse events compared with 17 cases in the placebo group (8.0% vs 26.0%, $P = .031$). Despite the very positive findings from this study, the trial was small and the treatment effect appears very large (69% relative risk reduction), which is inconsistent with the results from other RCTs of statins in preventing cardiovascular events.

α -2-Adrenergic agonist therapy

α -2-Adrenergic agonists, such as clonidine, can be used in those intolerant to β -blocker therapy and have been shown to significantly reduce perioperative myocardial ischemia

and postoperative death.⁴⁵

Aspirin therapy

Aspirin, as an anti-inflammatory and antiplatelet medicine, has been widely used for long-term prevention of cardiovascular disease. However, in perioperative medicine, there are still no data to support use of aspirin to prevent PMI. Periprocedural withdrawal of aspirin may increase cardiovascular complications including ACS, but continuing aspirin increases perioperative bleeding by about 1.5 fold.⁴⁶ Preoperative and early postoperative aspirin therapy has been reported to improve postoperative outcomes in patients undergoing CABG.^{47,48} In patients with vascular surgery, Robless et al⁴⁹ conducted a meta-analysis of clinical trials of antiplatelet therapy and found that aspirin reduced the incidence of myocardial infarction, stroke, and vascular death but the benefit did not reach statistical significance. In contrast, in a large, multinational RCT on aspirin therapy as prophylaxis for patients undergoing hip fracture surgery, ischemic cardiac events (myocardial infarction or death) were found to be higher among patients who received aspirin than placebo (hazard ratio 1.33, P = .05).⁵⁰

Despite the progress that has been made, several recent clinical trials (MaVS study,⁵¹ DIPOM trial,⁵² and POBBLE trial⁵³) have failed to demonstrate the use of β -blockers in the reduction of perioperative cardiac complications, and raised questions: Where did we go wrong and shall we reverse the ACC/AHA recommendations on perioperative β -blockers?⁵⁴ Further clinical trials (ie, POISE trial,⁵⁵ and DECREASE-IV study⁵⁶) are ongoing, which may or may not clarify these controversies because the target population, the choice of β -blockers, surgical procedures, and other options of the therapy may be different. In addition, it should be appreciated that even superbly designed RCTs may be inapplicable to large numbers of patients because the patients enrolled may not represent the patient population or the patients excluded would normally receive the treatment of interest. Nevertheless, those trials will certainly have important implications on whether or how to give β blockers to perioperative patients.

In the broad field of clinical medicine, previous clinical trials have clearly demonstrated that β -blockers provide multiple benefits to patients with CAD and heart failure, such as decreasing mortality in patients with acute myocardial infarction, secondary prevention of myocardial infarction in post-myocardial infarction patients, significant reduction in arrhythmic death or cardiac death in post-myocardial infarction patients, and improving survival in patients with heart failure.⁵⁷ In a recent multinational cohort study that included 44372 patients with ACS in 14 countries, Fox et al⁵⁸ demonstrated that improvements in the management of patients with ACS, including increases in use of β -blockers, are accountable for a significant decline in rates of new heart failure and mortality and in rates

of stroke and myocardial infarction at 6 months. In the field of surgery and anesthesiology, Lindenauer et al⁵⁹ conducted a very large retrospective cohort study including 663635 patients from 329 hospitals throughout the United States. In this study, they found that perioperative administration of β -blockers was associated with a reduced risk of death in the hospital among high-risk, but not low-risk, patients undergoing major noncardiac surgery, indicating a potential interaction between the effect of β -blockers and the extent of CAD risk.

Because of the overwhelming number of studies, some with conflicting results, we probably should consider the evidence in 2 dimensions, internal validity (RCTs) and external validity (retrospective and/or observational studies), and recognize that different methods may complement one another. Thus, the intervention adapted ideally should be supported by evidence with both high internal and high external validity.

In summary, either β -blockers or prophylactic coronary revascularization more likely would provide cardiac protection in select patient populations, that is, β -blockers for patients with intermediate-risk and stable CAD, and prophylactic coronary revascularization for patients with high risk of CAD. On the other hand, statins have proven their therapeutic value for a wide range of patients with CAD; up to now, statins have also appeared to provide cardiac protection for surgical patients. Nevertheless, given that the present RCTs with statins in surgical patients is limited to one small trial in which ≤ 100 patients have actually been treated^{43,44} and given that ACC/AHA/National Heart, Lung, and Blood Institute clinical advisory on the use and safety of statins has concluded that it may be prudent to withhold statins during hospitalization for major surgery because of potential side effects such as myopathy,⁶⁰ it is still premature to recommend the routine use of statins for all surgical patients with cardiac risk.

Years have passed since the cardiac risk index was proposed in 1977; however, the PMI conundrum continues. The pathogenetic mechanisms responsible for PMI remain a mystery, which hinders us greatly from developing effective clinical strategies to prevent/ reduce PMI.

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