Perioperative Cardiovascular Risk: Assessment and Management

Kenneth J. Tuman, MD

Cardiac events remain the primary cause of morbidity and mortality after elective surgery. The increasing age of the surgical population and an associated increase in the amount of preoperative cardiovascular disease indicate that perioperative cardiovascular morbidity will continue to be an important clinical problem. Many solutions have been proposed to reduce perioperative cardiovascular morbidity. This review summarizes what have been identified as appropriate methods for preoperative cardiac risk stratification and examines current knowledge about the management of perioperative cardiac risks in these patients.

Preoperative Risk Stratification

On the basis of aggregate knowledge from many investigations, certain clinical risk factors can be categorized on a spectrum from those highly associated with increased perioperative cardiovascular risk to those that are only minor predictors (1,2). The relative predictive weight of these factors is fairly consistent across studies and has led to a reasonably consistent classification of relative predictive value (Table 1). Although the presence of intermediate or major clinical predictors of cardiovascular risk is often used as part of the decision process for proceeding with noninvasive cardiac testing, an evaluation of functional capacity (itself a minor predictor) is also an essential component of deciding whether a patient should undergo such testing. In the presence of preexisting left ventricular dysfunction, even simple testing in medical patients, such as an evaluation of the distance that can be walked during a fixed time interval, provides nearly the same degree of predictive ability for death and exacerbation of chronic heart failure as quantification of ejection fraction (3). Limited exercise capacity is associated with a higher incidence of perioperative cardiovascular complications, especially in vascular surgical patients (4). In today's era of sophisticated technology, a careful patient history and physical examination (especially for signs of heart failure) remain key elements in assessing perioperative risk. Indeed, it has been recently suggested that a simple clinical assessment is the only risk-stratifying measure required for most patients being considered for major noncardiac surgery (5).

The predictive value of noninvasive testing is optimized when it is applied to patient populations with intermediate risk, since the number of false negatives and false positives is inversely proportional to disease prevalence. Consecutive rather than selective screening markedly reduces the positive predictive value and sensitivity of noninvasive testing, although negative predictive value remains high. Noninvasive cardiac testing is thus preferably considered for patients with intermediate clinical risk profiles to determine whether coronary angiography and revascularization should be performed before major noncardiac surgery (6). The relative value of different noninvasive tests remains controversial. When standard electrocardiographic exercise stress testing cannot be effectively applied (in patients with poor functional capacity or with an abnormal baseline electrocardiogram [ECG]), radionuclear stress perfusion scans (e.g., dipyridamole-thallium imaging) or stress echocardiography (with dipyridamole or dobutamine) can provide useful information to stratify preoperative cardiovascular risk and guide subsequent management. The evidence for benefit of preoperative evaluation with dipyridamole-thallium imaging or dobutamine stress echocardiography is most convincing in vascular surgical patients (6–8).

Two important questions about preoperative coronary angiography and subsequent coronary revascularization are whether this intervention actually improves aggregate perioperative morbidity and mortality and whether long-term morbidity and mortality are positively affected by this approach. Older data from the Coronary Artery Surgery Study registry indicate that coronary artery bypass grafting (CABG) performed before noncardiac surgery is associated with a reduced incidence of mortality and myocardial infarction compared with medical therapy in patients with significant coronary artery disease, although the combined mortality rate of the CABG procedure and the noncardiac surgery afterward showed no significant gain compared with proceeding with only medical management before noncardiac surgery (9). Subsequent follow-up of Coronary

Table 1. Clinical Predictors of Increased Perioperative Cardiovascular Risk

Major	
Unstable coronary syndromes	
Recent MI (≤30 days)	
Unstable or severe angina (Canadian Class III or IV)	
Decompensated congestive heart failure	
Significant arrhythmias	
High-grade atrioventricular block	
Symptomatic ventricular arrhythmias in presence of heart disease	
Supraventricular arrhythmias with uncontrolled ventricular rate	
Severe valvular disease	
Intermediate	
Mild angina (Canadian Class I or II)	
Prior MI by history or Q waves	
Compensated or prior congestive heart failure	
Diabetes mellitus	
Minor	
Advanced age	
Abnormal electrocardiogram (left ventricular hypertrophy, left bundle branch block, ST-T abnormalities)	
Rhythm other than sinus (e.g., atrial fibrillation)	
Low functional capacity (e.g., inability to climb one flight of stairs with a bag of groceries)[a]	
History of stroke	
Uncontrolled systemic hypertension	

See Ref. 2.
[a] Less than 4 metabolic equivalents.

Artery Surgery Study registrants undergoing high-risk noncardiac surgery is confirmatory of the short-term improvements in perioperative mortality and myocardial infarction (MI) compared with medical therapy alone (10). Published decision analyses have evaluated the effectiveness of preoperative coronary revascularization before noncardiac surgery (11,12). These analyses were sensitive to three probabilities: the prior probability of coronary artery disease, the risk of the revascularization procedure itself, and the risk of the noncardiac operation. Although the long-term mortality benefit was not assessed in these decision analyses, both confirmed that if the mortality of noncardiac surgery is intrinsically high (>5%), then preoperative catheterization (and revascularization by using CABG or percutaneous transluminal coronary angioplasty [PTCA]) is appropriate if the latter can be performed with low mortality. Conversely, if the intrinsic mortality risk attributable to the noncardiac procedure is low (or modest) and the mortality risk of the coronary revascularization procedure high, it is preferable to proceed directly to noncardiac surgery without revascularization. The latter analyses highlight the need to consider both the inherent risk of the noncardiac surgical procedure and the risks of coronary revascularization.

Surgical procedures can generally be classified into low, intermediate, and high risk, with high-risk procedures classically representing operations on the aorta and major peripheral vascular procedures, as well as intraabdominal and thoracic procedures that are lengthy and associated with significant fluctuations in circulating blood volume. Because of the frequent presence of ischemic heart disease, the question of preoperative coronary revascularization is often posed in vascular surgical patients. Ironically, the aggregate mortality of preoperative coronary revascularization in association with major vascular surgery may be the same if not greater than that associated with vascular surgery absent coronary intervention (13). Furthermore, proceeding with CABG before vascular surgery may only marginally reduce late cardiac deaths at 3–4 yr follow-up (13). This highlights the caveat that the recommendation to proceed with CABG before vascular surgery must be tempered by consideration of the risk factors that are predictive of morbidity and mortality after heart surgery. In particular, the consequences of peripheral vascular disease are notable because in-hospital mortality and the risk of serious complications after CABG are significantly greater in patients with peripheral vascular disease than in patients without vascular disease (14), and the noncardiac complications of cardiac surgery are markedly increased with advancing age (15). When considering CABG before major vascular surgery, the short-term combined morbidity and mortality of these two procedures must be carefully deliberated in relation to that expected with vascular surgery alone. It is probably best to reserve CABG for those high-risk patients with primary indications for CABG, on the basis of knowledge of patient subsets that exhibit long-term benefit (left main disease, three-vessel disease, two-vessel disease with proximal left anterior descending coronary artery disease, and decreased ejection fraction).

On the basis of current information about preoperative risk stratification, the following paradigm appears to be a useful approach to cardiac patients before noncardiac surgery (Fig. 1). Patients with low risk on the basis of clinical predictors can proceed directly to surgery regardless of the surgical procedure unless they have low functional capacity and a high-risk surgical procedure is planned, in which case noninvasive functional testing should be seriously considered. Patients with moderate risk on the basis of clinical predictors can go directly to surgery unless they are undergoing a high-risk surgical procedure or have poor functional capacity, in which case they should proceed to noninvasive testing. If noninvasive testing reveals large areas of myocardium at risk, coronary angiography and possible revascularization should be

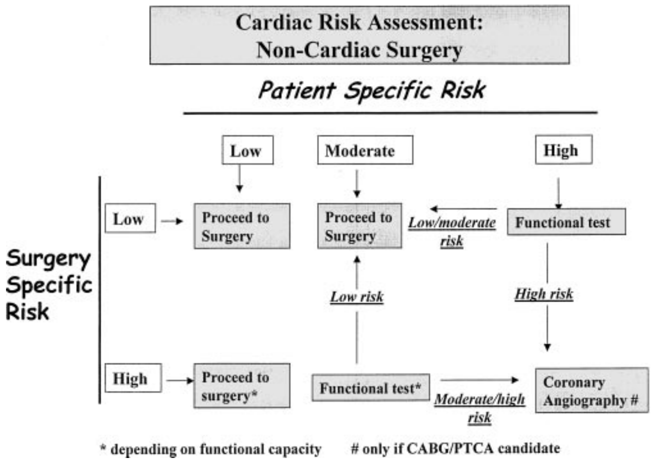

Figure 1. Simplified approach to preoperative cardiac assessment before noncardiac surgery, on the basis of consideration of both patient-specific and surgery-specific risks.

considered, but only if the patient is actually a candidate for CABG or angioplasty. If the functional noninvasive test results indicate a low risk for adverse cardiac outcome, such moderate-risk patients should go directly to the operating room. Patients who are high risk on the basis of clinical predictors should undergo functional testing even if they are undergoing low-risk surgical procedures. It may be appropriate in certain high-risk patients to proceed directly to coronary angiography if high-risk noncardiac surgery is contemplated, but only if they are candidates for CABG or PTCA and it is determined that they will benefit with either a significant reduction in short-term morbidity or mortality or, more important, that they will derive long-term outcome benefit. Of course, if the high-risk patient is not a candidate for coronary revascularization, it must be decided whether to proceed with the planned operation or whether consideration should be given to canceling or modifying the noncardiac surgical procedure to reduce short-term risk. Application of methods (described below) to reduce risk of cardiovascular complications is most important in the latter subset of high-risk patients. Finally, it is generally accepted that patients who have undergone successful coronary revascularization within 5 yr (or cardiac evaluation [either invasive or noninvasive] with favorable results within 2 yr) of the contemplated noncardiac procedure and who are functionally active without clinical evidence of ischemia have a lower likelihood of perioperative cardiac events and therefore do not require preoperative cardiac testing.

The data concerning risk reduction conferred by PTCA for myocardial revascularization before noncardiac surgery are not definitive. The reported series of patients with coronary angioplasty before noncardiac surgery are few and not tightly controlled, and they show variable efficacy in reducing MI and mortality after noncardiac surgery. Review of a large sample of Medicare patients suggests a clinically important short-term as well as longer-term outcome benefit of CABG compared with PTCA before major vascular surgery (16). Other data also cast some doubt on the efficacy of PTCA compared with CABG for reducing cardiovascular complications before noncardiac surgery and suggest that the impact of PTCA on perioperative risk is dependent on the timing before subsequent noncardiac surgery (17). The variability of the results of PTCA performed before elective surgery may be related to the interval of time between the revascularization procedure and the noncardiac surgery. There may be a window of opportunity for maximal risk reduction around elective surgery that starts several weeks after PTCA and extends for some months thereafter because during this interval, the coronary artery should have healed sufficiently to reduce the likelihood of spasm or thrombosis and yet not have recurrent stenosis. A high incidence of both major bleeding (related to mandatory antiplatelet regimens) and fatal coronary stent thrombosis has been reported after noncardiac surgery performed <6 wk after PTCA with coronary stenting (18).

Assessing the risk of perioperative cardiovascular complications also often involves a question of the timing of the noncardiac operation after a previous MI. Although historical data collected about two or three decades ago suggested a significant reduction in the rate of reinfarction if elective surgery were delayed for 6 mo, more recent data suggest that postponing surgery for this duration does not result in a meaningful decrease of reinfarction rate. In addition, although reinfarction mortality remains substantial, it is significantly improved compared with that reported in the past as part of the justification for the "6-month rule." The perioperative risk after previous MI appears to be related less to age of MI and more to the amount of residual myocardium at risk of significant ischemia and infarction, as well as the amount of preexisting left ventricular dysfunction. The risks of perioperative reinfarction and mortality may be significantly greater in a patient who has much at-risk myocardium at 8 mo after MI compared with a patient who has only a small amount of residual at-risk myocardium at 8 wk after MI. Advances in medical management have made the traditional high-risk time interval of 3–6 mo after MI less important, and no current benefit has been demonstrated for delaying surgery for 3–6 mo. It should be recognized that the "6-month rule" was based on <200 events collected over 25 yr. Importantly, current practice guidelines on perioperative cardiac evaluation define MI within <30 days as a major clinical predictor of risk, with high risk extending for a period of 6–8 wk, after which the previous MI represents an intermediate risk for perioperative cardiovascular complications (1,2).

Perioperative Management to Reduce Cardiac Risks

Once patients have been identified to be at increased risk of perioperative cardiac complications, especially those who will not undergo preoperative myocardial revascularization, management must be focused on strategies to reduce adverse cardiovascular outcomes. Whenever applicable, less invasive or less stressful procedures should be considered, especially if data validate that such approaches will actually reduce the incidence of complications. Examples of alternative procedures that allow surgical disease to be effectively addressed with reduced periprocedural risk include endovascular or extraanatomical approaches for revascularization of the arterial tree (19). Once the issues of preoperative evaluation, the need for coronary revascularization or modification of preoperative cardiac medications, the choice of type of surgery, and the timing of surgery have been addressed, a major focus of management is the modulation of adverse effects of perioperative stress, with the goal of preventing adverse outcome related to prolonged or severe ischemia.

A large body of knowledge about perioperative ischemia has been accumulated and provides a basis for several clinically important conclusions. There is a strong association of perioperative ischemia, especially postoperative ischemia, with adverse cardiovascular outcome. In general, most perioperative ischemia is a marker of disease and not necessarily a cause of myocardial infarction. Notably, most perioperative ischemia is not precipitated by hemodynamic events, although there is a substantial association with tachycardia. Coronary vasoconstriction has become recognized as an important mediator of ischemia, with modulation via the adrenergic, serotonergic, and prostanoid systems. The important role of coronary vasomotor tone is suggested by the observation of new thallium defects immediately after intubation in CABG patients despite normal (and unchanged) heart rate and blood pressure (20). Finally, it is now well recognized that postoperative ischemia is more frequent, more severe, and more significant in terms of clinical outcome than preoperative or intraoperative ischemia.

Although there is an overall association between ischemic events with adverse cardiac outcome, the duration and severity of ischemia appear to be particularly salient determinants. For example, Landesberg et al. (21) showed that the mean duration of ischemia was 21 min/hr vs 1 min/hr in patients with and without cardiac events after noncardiac surgery; these events were also associated with faster heart rates. Other data also suggest that postoperative episodes of ST segment depression lasting longer than 30 min are associated with cardiac events in high-risk patients undergoing noncardiac surgery (22). These observations suggest the importance of detecting ECG ischemia so that interventions can be directed at patients who exhibit prolonged or severe ischemia perioperatively. It should be recognized that contemporaneous visual observation of ECG traces on a oscilloscope detect only a minority of all ischemic episodes (23), suggesting the utility of ST segment trend monitors with appropriately preset alarm limits. Parenthetically, although transesophageal echocardiography-detected wall motion abnormalities have been shown to be sensitive markers of myocardial ischemia, one study has shown little incremental value for detecting ischemia beyond that provided by routine intraoperative ECG monitoring (24).

A number of interventions have been evaluated for reduction of adverse outcome related to prolonged or severe ischemia. Control of heart rate is particularly important because the rate threshold for ischemia is reduced as coronary vasomotor tone increases, so that oxygen demand can exceed supply at lower rates. This well established association between tachycardia and perioperative ischemia prompted the conduction of studies yielding convincing evidence that control of heart rate, especially using β-adrenergic blockade, is effective in reducing ischemia. More recent clinical studies have now demonstrated the efficacy of β-adrenergic blockade for improving outcome, including perioperative MI, in high-risk patients.

Stone et al. (25) demonstrated a significant reduction in the amount of ischemia noted during intubation when at-risk patients were treated with a single preoperative dose of β-blocker. A study published nearly a decade ago suggested an outcome benefit of perioperative β-blockade with a significant reduction in MI rate in the setting of elective abdominal aortic aneurysm surgery (26). More recently, the administration of preoperative β-blockade with continuation into the postoperative period has been associated with a reduced incidence of tachycardia as well as a significant reduction in the incidence of Holter ischemia on the first two postoperative days after major noncardiac surgery (27). Similarly, the administration of β-blocker before and after surgery has been associated with a reduction in cardiac mortality and serious cardiac events for up to 2 yr after discharge, confirming the impression that perioperative as well as longer-term postoperative β-blockade is beneficial (28). The latter study did not demonstrate an acute perioperative outcome benefit. A subsequent study of perioperative β-blockade applied this intervention only in patients undergoing high-risk vascular surgery with documented high cardiac risk defined by abnormal dobutamine stress echocardiography testing (in contrast to most other studies that also include patients "at risk" solely on the basis of clinical risk stratification) (29). The latter study demonstrated a profound reduction in adverse cardiac events perioperatively, prompting study discontinuation after interim analysis. Although the applicability of these findings to the broader population of at-risk patients will require additional studies, there appears to be sufficient current evidence to recommend perioperative β-blockade for cardiac risk reduction in high-risk patients.

Many clinicians are reluctant to administer β-adrenergic blockers to certain high-risk patients because of concerns about intolerance to potential cardiac depressive effects of β- blockade. Such concerns are illustrated by a recent study demonstrating that although β-blockade is extremely effective in elderly patients after acute MI (reducing 1-yr mortality by 14%), prescriptive rates for β-blockers vary widely among specialties and that overall, β-blockers are underused (30). β-Blockers are also associated with a 30%–40% reduction in the risk of death after acute MI, even in high-risk subsets, including the elderly, patients with prior MI, and even patients with low ejection fractions or preexisting chronic heart failure (31). Remarkably, β-blockade is of benefit even with coronary revascularization after MI (31).

The beneficial effects of other drugs to reduce serious perioperative cardiac morbidity have not been convincingly demonstrated. Improved control of heart rate and blood pressure and a reduction in perioperative myocardial ischemia have been demonstrated with use of α-2 agonists such as clonidine and mivazerol in high-risk patients, although no study has suggested more than a trend towards reduced MI rates (32,33). Calcium entry blockers are not effective in reducing the incidence of ischemia or controlling heart rate in at-risk patients (34). Although some data suggest that higher doses of prophylactic nitroglycerin are associated with a reduction in myocardial ischemia compared with lower doses, no study has shown any reduction in MI or death when prophylactic nitroglycerin is administered perioperatively (35).

In addition to controlling causes of demand ischemia, it is now recognized that perioperative alterations in coagulation, local forces on coronary artery plaques, and other factors are likely important determinants of adverse outcome in the perioperative setting. There is increased risk of myocardial events with markers indicating hypercoagulability, and it is well established that coagulation is generally stimulated perioperatively, with increases in markers that augment coagulability and decreases in moieties that serve to inhibit coagulation. Although there is evidence that attenuation of this hypercoagulability by epidural anesthesia or analgesia is associated with a reduced incidence of peripheral vascular graft thrombosis after infrainguinal revascularization (36,37), the data on the effects on cardiac complications are equivocal. Because of the known beneficial effects of aspirin for significantly reducing the risk of serious cardiovascular events in high-risk patients, low-grade perioperative anticoagulation may be beneficial in some high-risk patients. Despite concerns that the use of aspirin may increase perioperative bleeding, this is not universal and probably depends on the type of operation.

The level of hemoglobin can be an important myocardial oxygen supply factor in high-risk patients. Perioperative hematocrit levels of $<$28% have been independently associated with an increased risk of postoperative myocardial ischemia and cardiac events in high-risk surgical patients (38,39). In addition, even mild perioperative hypothermia is associated with an increased risk of postoperative ischemia, perhaps because of increased plasma norepinephrine and exaggerated vasoreactivity (40,41). Proactive maintenance of normothermia is associated with a reduced incidence of morbid cardiac events, including significant arrhythmias, in high-risk surgical patients (42).

Conclusions

The risks of noncardiac surgery have decreased during the last two to three decades, although patients with cardiac disease, especially ischemic heart disease, remain at greater risk of serious perioperative cardiovascular complications than the general population. The initial assessment of risk should be based on a stepwise approach that uses important clinical information from the history and physical examination, especially functional capacity and the interval from any previous invasive or noninvasive cardiac evaluation or myocardial revascularization. Using this information and considering the nature of the planned noncardiac surgery, a reasoned approach can be applied to the decision about whether to pursue further cardiac evaluation or intervention or proceed directly to the planned noncardiac surgery (Fig. 1). Once the decision has been made to proceed with the noncardiac procedure, methods of modifying perioperative cardiac risk should be applied, especially β-adrenergic blockade. Current data convincingly demonstrate the benefit of controlling adverse adrenergic responses both during and after surgery. Undoubtedly, future practice will continue to focus on risk recognition and selective application of preoperative testing in high-risk populations while seeking to develop consensus on selective perioperative monitoring strategies.

Finally, despite the general utility of the outlined approach, management strategies must be tailored for the individual patient to achieve efficacy and cost-effectiveness.

References

1. Eagle K, Brundage B, Chaitman B, et al. Guidelines for perioperative cardiovascular evaluation of noncardiac surgery: a report of the American Heart Association/American College of Cardiology Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures. Circulation 1996;93: 1278–317.
2. American College of Physicians. Guidelines for assessing and managing the perioperative risk from coronary artery disease associated with major noncardiac surgery. Ann Intern Med 1997;127:845–50.
3. Bittner V, Weiner DH, Yusuf S, et al. Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction: SOLVD investigators. JAMA 1993;270: 1702–7.
4. McPhail N, Calvin JE, Shariatmadar A, et al. The use of preoperative exercise testing to predict cardiac complications after arterial reconstruction. J Vasc Surg 1988;7:60–8.
5. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major non-cardiac surgery. Circulation 1999;100: 1043–9.
6. Eagle KA, Coley CM, Newell JB, et al. Combining clinical and thallium data optimizes perioperative assessment of cardiac risk before major vascular surgery. Ann Intern Med 1989;110: 859–66.
7. Mantha S, Roizen ME, Barnard J, et al. Relative effectiveness of perioperative tests for predicting adverse cardiac outcomes after vascular surgery: a meta-analysis. Anesth Analg 1994;79:422–33.
8. Shaw LJ, Eagle KA, Gersh BJ, Miller DD. Meta-analysis of intravenous dipyridamole thallium-201 imaging (1985–1994) and dobutamine echocardiography (1991–1994) for risk stratification before vascular surgery. J Am Coll Cardiol 1996;1985;27: 787–98.
9. Foster ED, Davis KB, Carpenter JA, et al. Risk of noncardiac operation in patients with defined coronary disease: the Coronary Artery Surgery Study (CASS) registry experience. Ann Thorac Surg 1986;41:420–50.
10. Eagle KA, Rihal CS, Mickel MC, et al. Cardiac risk of noncardiac surgery: influence of coronary disease and type of surgery in 3368 operations. Circulation 1997;96:1882–7.
11. Fleisher LA, Skolnick ED, Holroyd KJ, Lehmann HP. Coronary artery revascularization before abdominal aortic aneurysm surgery: a decision analytic approach. Anesth Analg 1994;79: 661–9.
12. Mason JJ, Owens DK, Harris RA, et al. The role of coronary angiography and coronary revascularization before noncardiac surgery. JAMA 1995;273:1919–25.
13. Massie MT, Rohrer MJ, Leppo JA, Cutler BS. Is coronary angiography necessary for vascular surgery patients who have positive results of dipyridamole thallium scans? J Vasc Surg 1997;25:975–82.
14. Rihal CS, Sutton-Tyrrell K, Schaff HV, et al. Increased incidence of complications among patients with peripheral vascular disease following coronary bypass grafting or angioplasty. Circulation 1997;96:467–8.
15. Tuman KJ, McCarthy RJ, Najafi H, Ivankovich AD. Differential effects of advanced age on neurologic and cardiac risks of coronary artery operations. J Thorac Cardiovasc Surg 1992;104: 1510–7.
16. Fleisher LA, Eagle KA, Shaffer T, Anderson GF. Perioperative and long-term mortality rates after major vascular surgery: the relationship to preoperative testing in the medicare population. Anesth Analg 1999;89:849–55.
17. Posner KL, van Norman GA, Chan V. Adverse cardiac outcomes after noncardiac surgery in patients with prior percutaneous transluminal coronary angioplasty. Anesth Analg 1999; 89:553–60.
18. Katuza GL, Joseph J, Lee JR, et al. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. J Am Coll Cardiol 2000;35:1288–94.
19. Kirby L, Rosenthal D, Atkins C, et al. Comparison between the transabdominal and retroperitoneal approaches for aortic reconstruction in patients at high risk. J Vasc Surg 1999;30:400–6.
20. Kleinman B, Henkin RE, Glisson SN, et al. Qualitative evaluation of coronary flow during anesthetic induction using thallium-201 perfusion scans. Anesthesiology 1986;64:157–64.
21. Landesberg G, Luria MH, Cotev S, et al. Importance of long-duration postoperative ST-segment depression in cardiac morbidity after vascular surgery. Lancet 1993;341:715–9.
22. Fleisher LA, Nelson AH, Rosenbaum SH. Postoperative myocardial ischemia: etiology of cardiac morbidity or manifestation of underlying disease. J Clin Anesth 1995;7:97–102.
23. Biagnini A. Unreliability of conventional visual electrocardiographic monitoring for detection of transient ST segment changes in a coronary care unit. Eur Heart J 1984;61:193–6.
24. Eisenberg MJ, London MJ, Leung JM, et al. Monitoring for myocardial ischemia during noncardiac surgery: a technological assessment of transesophageal echocardiography and 12-lead electrocardiography. JAMA 1992;268:210–6.
25. Stone JG, Foex P, Sear JW, et al. Myocardial ischaemia in untreated hypertensive patients: effect of a single small oral dose of a β-adrenergic blocking agent. Anesthesiology 1988;68: 495–500.
26. Pasternack PF, Imparato AM, Baumann FG, et al. The hemodynamics of β-blockade in patients undergoing abdominal aortic aneurysm repair. Circulation 1987;76:III1–7.
27. Wallace A, Layug B, Tateo I, et al. Prophylactic atenolol reduces postoperative myocardial ischemia. Anesthesiology 1998;88: 7–17.
28. Mangano DT, Layug EL, Wallace A, et al. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery: Multicenter Study of Perioperative Ischemia Research Group. N Engl J Med 1996;335:1713–20.
29. Poldermans D, Boersma E, Bax JJ, et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. N Engl J Med 1999; 341:1789–94.
30. Krumholz HM, Radford MJ, Wang Y, et al. National use and effectiveness of β-blockers for the treatment of elderly patients after acute myocardial infarction: National Cooperative Cardiovascular Project. JAMA 1998;280:623–9.
31. Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. N Engl J Med 1998;339:489–97.
32. Stuhmeier KD, Mainzer B, Cierpka J, et al. Small, oral dose of clonidine reduces the incidence of intraoperative myocardial ischemia in patients having vascular surgery. Anesthesiology 1996;85:706–12.
33. McSPI-Europe Research Group. Perioperative sympatholysis: beneficial effects of the α 2-adrenoceptor agonist mivazerol on hemodynamic stability and myocardial ischemia. Anesthesiology 1997;86:346–66.
34. Slogoff S, Keats AS. Does chronic treatment with calcium entry blocking drugs reduce perioperative myocardial ischemia? Anesthesiology 1988;68:676–82.
35. Coriat P, Daloz M, Bousseau D, et al. Prevention of intraoperative myocardial ischemia during noncardiac surgery with intravenous nitroglycerin. Anesthesiology 1984;61:193–6.
36. Tuman KJ, McCarthy RJ, March RJ, et al. Effects of epidural anesthesia and analgesia on coagulation and outcome after major vascular surgery. Anesth Analg 1991;73:696–704.
37. Christopherson R, Beattie S, Frank, et al. Perioperative morbidity in patients randomized to epidural or general anesthesia for lower extremity vascular surgery. Anesthesiology 1993;79: 422–34.

38. Nelson AH, Fleisher LA, Rosenbaum SH. Relationship between postoperative anemia and cardiac morbidity in high-risk vascular patients in the intensive care unit. Crit Care Med 1993;21: 860–6.
39. Hogue CW, Goodnough LT, Monk TG. Perioperative myocardial ischemic episodes are related to hematocrit level in patients undergoing radical prostatectomy. Transfusion 1998;38:924–31.
40. Backlund M, Lepantalo M, Toivonen L, et al. Factors associated with post-operative myocardial ischaemia in elderly patients undergoing major non-cardiac surgery. Eur J Anaesthesiol 1999; 16:826–33.
41. Frank SM, Fleisher LA, Breslow MJ, et al. Unintentional hypothermia is associated with postoperative myocardial ischemia. Anesthesiology 1993;78:468–76.
42. Frank SM, Fleisher LA, Breslow MJ, et al. Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events: a randomized clinical trial. JAMA 1997;277:1127–34.