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Perioperative β-Adrenergic Receptor Blockade

Physiologic Foundations and Clinical Controversies

Martin J. London, M.D., Michael Zaugg, M.D., D.E.A.A.,† Marcus C. Schaub, M.D., Ph.D.,‡ Donat R. Spahn, M.D., F.R.C.A.§*

THE recent focus on perioperative β-adrenergic receptor blockade (PBB) to reduce cardiac morbidity or mortality follows nearly 40 yr of research documenting the cardioprotective effects of β-adrenergic receptors (BARs). On the basis of two influential randomized controlled trials demonstrating improvement in perioperative (30-day) or long-term (1- to 2-yr) outcome in high-risk patients, this practice is now routinely recommended by consultants and has recently been highlighted as a "top-tier" patient safety practice by the Institute of Medicine.[1] As such, it may serve as a performance measure for quality improvement. However, many aspects remain controversial.[2]

This commentary examines physiologic concepts and potential uses of PBB in patients undergoing noncardiac surgery. Given well-documented difficulties with guideline compliance for β blockade after acute myocardial infarction (MI) (secondary prevention), it is to be expected that similar attempts in the large pool of eligible perioperative patients will require substantial ongoing efforts.

The Problem of Perioperative Cardiac Morbidity

Perioperative cardiac morbidity and mortality exact a substantial human toll and consume constrained economic resources. Their magnitude and costs are controversial, particularly in the general surgical population, given the variability in diagnosis and coding of outcomes. However, they are largely considered to be preventable with appropriate risk stratification, selective use of myocardial revascularization, and appropriate cardioprotective therapies, such as PBB.[3]

Since the 1970s, the timing and character of perioperative myocardial infarction (PMI) reported in the literature has shifted from a predominance of Q-wave MI peaking between postoperative days 2 and 3 with a high mortality (25–50%) to earlier-occurring non–Q-wave MI with lower mortality.[4] PMI is closely associated with sustained elevation of heart rate, an absence of chest pain, and prolonged premonitory episodes of ST-segment depression before overt MI.

Perioperative hypothermia, anemia, increase of circulating catecholamines, and endogenous vasoconstrictors are etiologic factors. Abnormal endothelial function due to acute inflammatory responses is a well-recognized factor in the medical setting but is poorly characterized in the surgical setting. Easily inducible myocardial ischemia on provocative testing is strongly predictive of PMI. Impaired ventricular function markedly increases risk, likely because of reduction in coronary perfusion pressure. Asymptomatic perioperative troponin leaks may identify patients who are at increased risk in the first 6–24 months postoperatively.[5]

Cardiovascular Effects of β Blockade

The impact of PBB on myocardial oxygen balance depends on complex interactions between supply-and-demand variables, anatomic factors (*e.g.*, coronary stenoses, myocardial function), and the physiologic milieu (fig. 1).

The major salutary effects are reductions in heart rate (increasing diastolic perfusion time) and contractility (reducing oxygen demand). Diastolic time is curvilinearly related to heart rate, increasing rapidly below 75beats/min. As left ventricular coronary perfusion occurs predominantly during diastole, coronary blood flow increases, particularly distal to coronary stenoses and in the metabolically active subendocardium. Reducing heart rate directly decreases oxygen demand *via* reversal of the Bowditch-Treppe effect (*e.g.*, increasing contractility with increasing heart rate). Maintenance of adequate coronary perfusion pressure is also important.

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* Professor of Clinical Anesthesia, Department of Anesthesia and Perioperative Care, University of California, San Francisco. † Director, Cardiovascular Anesthesia Laboratory, Institute of Anesthesiology, University Hospital Zurich, and Institute of Pharmacology and Toxicology, University of Zurich. ‡ Professor of Pharmacology, Department of Pharmacology and Toxicology, University of Zurich. § Professor and Chairman, Department of Anesthesiology, University Hospital, Lausanne.

Received from the Department of Anesthesia and Perioperative Care, University of California, San Francisco, California; the Cardiovascular Anesthesia Laboratory, Institute of Anesthesiology, University Hospital Zurich, Zurich, Switzerland; the Institute of Pharmacology and Toxicology, University of Zurich, Zurich, Switzerland; and the Department of Anesthesiology, University Hospital, Lausanne, Switzerland. Submitted for publication February 21, 2003. Accepted for publication July 11, 2003. The work of Drs. Zaugg and Schaub is supported by the Swiss Heart Foundation and grant No. 3200-063417 from the Swiss National Science Foundation, Berne, Switzerland.

Address correspondence to Dr. London: Anesthesia (129), Veterans Affairs Medical Center, 4150 Clement Street, San Francisco, California 94121-1598. Address electronic mail to: londonm@anesthesia.ucsf.edu.

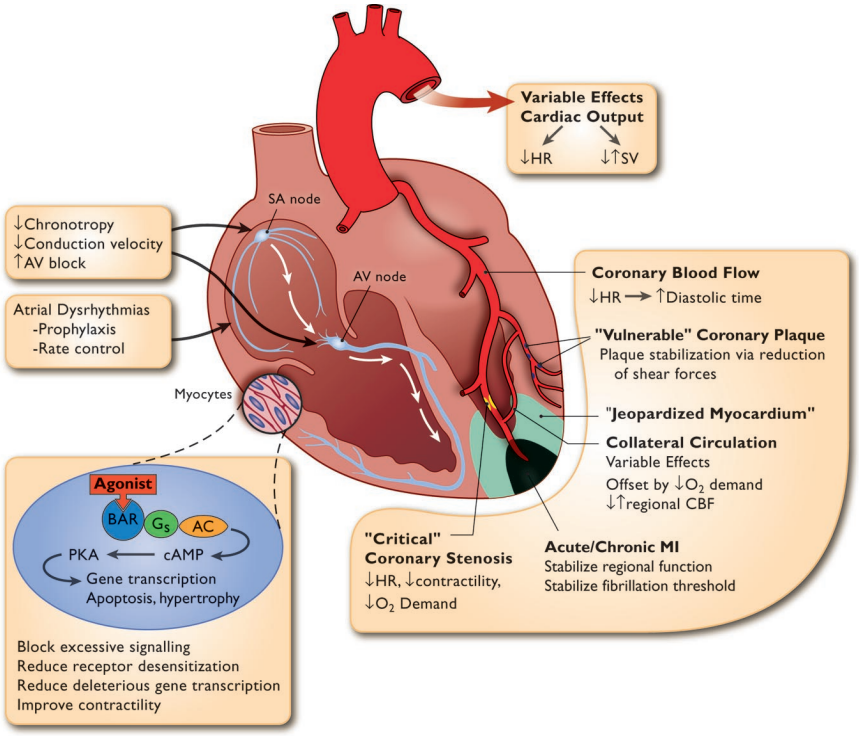

Fig. 1. Potential cardiovascular effects of perioperative β-adrenergic receptor (BAR) blockade. The major well-appreciated clinical effects and newer contemporary documented or strongly suggested effects of BAR blockade on the heart are depicted. AC = adenylyl cyclase; AV = atrioventricular; cAMP = cyclic adenosine monophosphate; CBF = coronary blood flow; G_S = stimulatory G protein; HR = heart rate; MI = myocardial infarction; O_2 = oxygen; PKA = protein kinase A; SA = sinoatrial; SV = stroke volume.

Reduction in contractility reduces demand but may increase end-diastolic pressure in the failing ventricle. Low-dose β blockade for angina pectoris has modest effects on blood pressure in euvolemic medical patients. In surgical patients receiving sympatholytic therapies, greater reduction is likely.

Amelioration of ischemia distal to a critical stenosis is also influenced by the collateral circulation. The effects of β blockade on it remain controversial. Little change in regional blood flow may occur because of an overall reduction in oxygen demand. β Blockers have little influence on the primary variables influencing plaque vulnerability (*e.g.*, lipid accumulation, inflammation, matrix degradation, and others). However, they reduce mechanical stress *via* hemodynamic effects, and clinical data support protective associations, particularly in patients with left ventricular hypertrophy.[6] Patients with dyslipidemias, glucose intolerance, and obesity have higher rates of recurrent plaque rupture predisposing to sudden death.[7]

β Blockers have potent antiarrhythmic effects, particularly in the setting of acute ischemia. Reduction in circulating free fatty acids *via* inhibition of lipolysis may protect against ventricular fibrillation. They reduce sudden cardiac death in patients with congestive heart failure (CHF). Their prophylactic properties and enhanced rate control in atrial dysrhythmias are beneficial perioperatively.

Autonomic Nervous System and Receptor Physiology

Membrane-bound BARs (β_1, β_2, and the inhibitory β_3 receptor) interact with agonists to mediate signal transduction. Physiologic specificity is modulated by a variety of protein kinases.[8] Stimulation of the mitogen-activated protein kinase signaling cascade affects gene transcription, inducing cardiac hypertrophy and apoptosis. Sustained agonist stimulation causes receptor desensitization *via* phosphorylation within minutes. Prolonged desensitization may occur with receptor sequestration. Human myocardium relies on BAR stimulation (predominantly β_1) to increase contractility during stress. Changes in receptor type, density, and sensitivity with CHF markedly reduce myocardial adrenergic signal transduction capability. Antagonism of excessive BAR stimulation increases this and thus forms the basis for primary treatment of CHF.[9]

Receptor physiology with myocardial ischemia is controversial given the heterogeneity of coronary syndromes. Increases in systemic concentrations and regional accumulation of catecholamines during acute MI likely facilitates myocardial necrosis. BAR density may increase acutely, causing supersensitivity that precipitates ventricular fibrillation. Complex interactions between β and α receptors are now appreciated. Imbalance in α- and β-adrenergic signaling due to concurrent

receptor polymorphisms has recently been identified as a risk factor for CHF.[10]

Perioperative studies document acute BAR desensitization in peripheral lymphocytes up to a week postoperatively, variably associated with sympathetic activation. Acute β blockade before cardiopulmonary bypass may protect ventricular function by inhibiting receptor desensitization. However, further research is needed to confirm that acute PBB uniformly protects ventricular function in the perioperative period.

Other Physiologic Effects of β Blockade

The anesthesia-sparing effects of PBB have been exploited clinically. In elderly men undergoing abdominal surgery, perioperative atenolol reduced hemodynamic lability, facilitated faster recovery, and lowered analgesic requirements.[11] However, direct effects on hemodynamics *versus* a true effect on anesthetic requirement remain controversial. Lipophilic β blockers readily cross the blood–brain barrier and have traditionally been implicated in central nervous system side effects. However, recent data cast doubt on the specificity and magnitude of these effects. β Blockers may alter memory encoding for and impart neuroprotective effects during cerebral ischemia as well.[8]

Critical Analysis of the Major Randomized Controlled Trials

Not until the 1990s, when enhanced perioperative or long-term survival were reported, did PBB enter the realm of evidence-based medicine.[2] However, limited physiologic data collection, most notably, markers of the stress response or delineation of ventricular function, have frustrated attempts to determine casual mechanisms for the benefits observed.

The studies of Mangano *et al.*[12] and Poldermans *et al.*[13] have generated the most interest and debate. The latter is less controversial given its highly selected cohort (vascular patients with inducible ischemia) likely explaining the observed 90% relative reduction in 30-day outcome. Nonetheless, a lack of blinding, use of a standard care comparison, and an unexpectedly high mortality rate from PMI are problematic. A retrospective analysis of the screened cohort (1,351 patients), correlating clinical predictors, dobutamine stress echo results, and β blocker use (primarily long-term oral use with only 5% specifically treated acutely) with clinical outcomes, suggests that patients receiving *any* β blocker accrued benefit as the number of clinical predictors or new wall motion abnormalities increased.[14] However, the protective effect was negligible in the highest-risk patients, most of whom underwent surgical revascularization. Identifying (and treating) the latter group remains controversial, although the presence of three or more revised cardiac risk index predictors is recommended as a threshold to institute provocative testing.[2] The efficacy of PBB in this retrospective analysis remains controversial given the low overall event rate (3.3%) and uncertainty of the "intensity" of PBB. Other observational studies reporting associations of long-term oral therapy *alone* with outcome have not shown significant benefits.

The efficacy of long-term PBB in the cohort of Poldermans *et al.*[15] was confirmed by prospective follow-up. Whether long-term use is efficacious in all vascular patients in the absence of other American College of Cardiology/American Heart Association (ACC/AHA) guideline criteria is uncertain. It seems that compliance with multiple guideline parameters is needed to ensure long-term survival.[16]

The study of Mangano *et al.* is more controversial given a wider variety of patients and procedures studied, limited risk stratification, an earlier time frame before ambulatory or laparoscopic surgery or use of aggressive pain control and regional analgesia, the use of a single hospital, potential imbalances in patient risk between groups, lack of consideration of subsequent surgical procedures, and other factors.[12] They observed a striking reduction in long-term outcome (approximately 65% relative risk reduction, primarily in the first year) in the absence of a difference in perioperative outcome. This occurred despite a significantly greater amount of early postoperative myocardial ischemia on ambulatory ST-segment monitoring in patients who received placebo, a finding inconsistent with earlier reports from this group of a very strong association of postoperative ischemia with early PMI.[17] It has been speculated that inadequate statistical power or unexplained physiologic mechanisms (*e.g.*, increased catecholamine concentrations leading to delayed rupture of coronary plaques) may be responsible. Multivariate analysis revealed only two significant variables associated with long-term survival: diabetes (adverse) and atenolol therapy (protective).[12] However, evaluation of subgroups of clinical interest (known coronary artery disease [CAD] *vs.* risk factors only, vascular *vs.* other types of surgery, and others) is problematic because of the limited sample size. Effects of sex were not evaluated (all-male cohort), nor was regional anesthesia or analgesia. Given these limitations, ACC/AHA guidelines accord PBB use in this type of cohort a class IIa recommendation in contrast to class I for patients meeting the entry criteria of Poldermans.[3] However, because this protocol is logistically simpler, it is appealing to a wide variety of settings.

An intriguing observation is the small difference in mean heart rates between treated and placebo (Mangano *et al.*[12]) or standard care (Poldermans *et al.*[13]) groups, on the order of 10–15 beats/min (depending on the time period reported), ranging from the low 70s to the mid to high 80s. This contrasts with earlier studies indicating that heart rates of greater than 100 beats/min are most predictive of ischemia. If the prevailing hypothesis linking ischemic episodes, heart rate, and ultimate outcome

is correct, identifying patients based on maintenance of a group mean (*e.g.*, target) heart rate alone does not seem possible. Raby *et al.*[18] have suggested that identification of the preoperative ischemic threshold on ambulatory monitoring is possible. However, this approach is logistically difficult if not impossible. The observation that 35% of atenolol-treated patients in the cohort of Mangano *et al.* had intraoperative tachycardia suggests that a longer period of preoperative therapy, more aggressive dosing, or additional anesthetic interventions were required.[17]

The interaction of PBB with regional anesthesia or analgesia has not been well characterized, despite epidural use (type and duration unspecified) in 40% of patients in the cohort of Poldermans *et al.* Given the strong interest in cardioprotective effects of regional anesthesia (particularly by the thoracic epidural route), this warrants further investigation.

It has been suggested that PBB may decrease subclinical cardiac troponin (I or T) release, leading to improved long-term outcome.[11] However, limited perioperative and percutaneous coronary intervention data are inconclusive or conflicting.[5]

It can be argued that given strong efficacy in secondary prevention after MI, additional perioperative studies are unnecessary. That short-term PBB is beneficial or neutral in patients with known CAD is not controversial. In many centers, increasing percentages of patients present on long-term therapy because of better compliance with ACC/AHA guidelines. Although not all are adequately β blocked, most can be easily treated with routine anesthetic care and low-dose intravenous supplementation.

There is greater controversy in the larger group of patients with CAD risk factors only, in whom the number needed to treat to achieve a beneficial effect is a major concern. Numbers needed to treat ranging from only 3.2 for Poldermans *et al.* to 8.3 for Mangano *et al.* for mortality or PMI are strikingly lower than a recent meta-analysis estimate of 42 for secondary prevention after MI (2-yr mortality).[2,19] Specific numbers needed to treat for the risk factor–only group were not reported and are likely to be substantially greater.

Logistics of Perioperative β Blockade

Few patients have absolute contraindications to PBB. Although older literature warns against use with any degree of reactive airway disease (*e.g.*, precipitation of bronchospasm), insulin-dependent diabetes (*e.g.*, masking signs of hypoglycemia), and even peripheral vascular disease (*e.g.*, increase in peripheral vascular resistance due to unopposed α-adrenergic vasoconstriction), newer data suggest that careful titration of β_1-selective agents is tolerated in many of these patients.[20] However, severe asthma or a strong reactive component with chronic obstructive lung disease remain strong contraindications, as does major conduction disease (in the absence of a pacemaker) and previous documented sensitivities. In some patients, other sympatholytic therapies, including α_2 agonists or continuous regional techniques, may be considered. Patients with compensated CHF may tolerate PBB, although it should be instituted gradually before surgery in accordance with ACC/AHA CHF guidelines. Judicious intravenous supplementation is usually well tolerated, especially during periods of adrenergic stimulation. Patients with isolated diastolic dysfunction are less problematic.

Increased vigilance is indicated in elderly patients given the reduction in maximal heart rate responses, lower resting heart rate, reduced ventricular compliance, and other physiologic changes of aging. Racial variation in response to β blockade has been reported as a result of genetic polymorphism of receptors or enzyme systems. Blacks may respond less favorably to treatment for CHF or hypertension (but not for CAD). Debrisoquin oxidation polymorphisms of metoprolol in Asian populations are common. There is little evidence for sex-specific effects.

Acute PBB with hypovolemia or sepsis is potentially hazardous. Patients receiving long-term therapy, especially with normal ventricular function, tolerate moderate degrees of hypovolemia well. Responses in patients with impaired ventricular function or concurrent regional sympathectomy are likely to be inadequate. A potential clinical strategy is to use esmolol after the period of major bleeding and after restitution of blood or plasma volume.

Secondary prevention studies have not documented differences in outcomes between agents with varying receptor selectivity or lipophilicity (so-called class differences), with the exception of an adverse association in agents with intrinsic sympathomimetic activity.[19] However, PBB should be instituted using β_1-selective agents (*e.g.*, atenolol, metoprolol, bisoprolol) given a lower potential for side effects at routine clinical doses. With increasing dosage, receptor selectivity is lost.

The ACC/AHA Perioperative Guidelines Committee limits specific recommendations to use in patients with inducible ischemia, starting days to weeks before surgery, titrated to a resting heart rate from 50–60 beats/min preoperatively.[3] No specific recommendations are made for lower-risk patients or for intraoperative or postoperative therapy.

Preoperative oral therapy may allow assessment of tolerance to therapy and take advantage of cellular-level effects (manifested *via* effects on gene transcription).[8] However, this remains speculative, and there are no data showing that acute PBB is less effective or less safe. Resting heart rate alone is an imprecise marker of β blockade, which is most accurately assessed by response to exercise or direct adrenergic challenge. Therefore, some patients may need substantial intravenous supplementation.

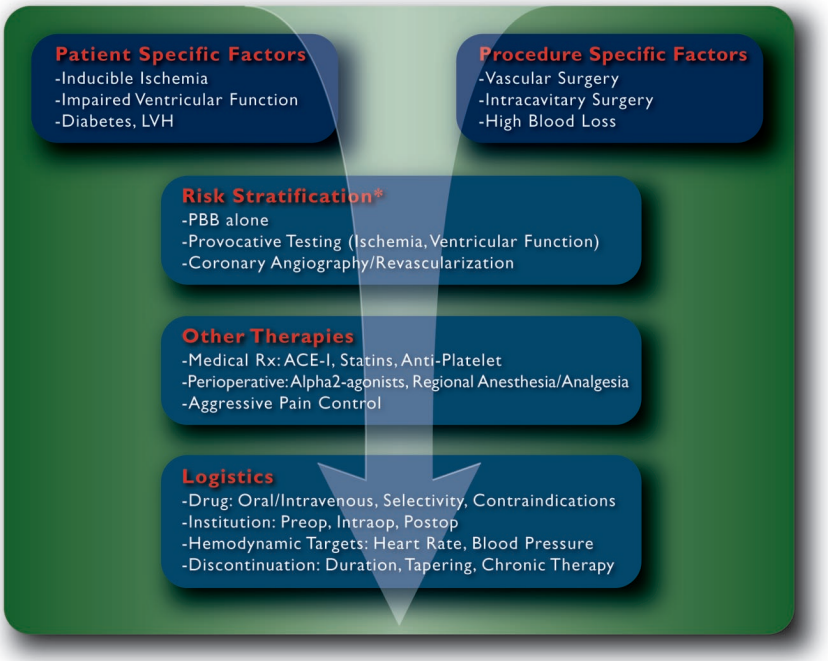

Fig. 2. Clinical and logistical issues with perioperative β-adrenergic receptor blockade (PBB). Major clinical and logistical issues facing the clinician in the use of PBB. * Some components of risk stratification may be deferred until after surgery in lower-risk patients (including many amenable to PBB), or the need for long-term risk stratification may first be recognized in the postoperative period. ACE = angiotensin-converting enzyme; LVH = left ventricular hypertrophy; Rx = treatment.

Institution of PBB before induction of anesthesia may not be required if hemodynamics are well controlled. This contrasts to emergence when ischemia is particularly common. Provision of the most aggressive therapy during the first 48–72 h postoperatively is likely to provide maximal benefit. The adequacy of pain control and other physiologic abnormalities (*e.g.*, fever, anemia) are important variables in the duration of therapy. It is reasonable for therapy in low- to moderate-risk cohorts to be continued for the first week postoperatively, whereas patients undergoing vascular surgery, with its higher event rate, are likely better treated with therapy for 14–30 days postoperatively.

Ideally, oral therapy should be tapered before discontinuation to minimize hyperadrenergic withdrawal responses. Well documented in the medical literature, these are infrequently reported perioperatively, likely because of the short duration of treatment and the low doses used. Tapering is not usually required for doses of less than 25 mg oral atenolol (or its equivalent).

Adequate systemic blood pressure must be maintained. A systolic pressure of 100 mmHg or greater is recommended, although higher pressures are required in older or compromised patients. Studies have reported acceptable levels of hemodynamic side effects (primarily bradycardia and hypotension requiring transient treatment). However, safety data in specific subgroups, particularly with high levels of sympathetic blockade, major blood loss, advanced age, or other cardiac medications, have not been well delineated.

Careful attention is required when using atenolol in patients with renal insufficiency, particularly with repeated intravenous dosing, given its exclusive renal elimination and long half-life. Bisoprolol, metabolized by hepatic and renal routes, is not available intravenously and therefore is less problematic.

Finally, the perioperative period offers a unique opportunity for anesthesiologists to enhance compliance with ACC/AHA treatment guidelines for β blocker use (*e.g.*, ischemic heart disease, CHF, and dysrhythmias). Therefore, reasonable attempts should be made to facilitate continuation of therapy in appropriate patients to maximize long-term survival.

Conclusions

Evidence for the efficacy of PBB is strong, and new physiologic and clinical data continue to accumulate. Epidemiologic studies provide a framework for the clinician to apply new physiologic principles in patients with known CAD and those at risk, particularly those with diabetes and left ventricular hypertrophy. Within the larger paradigm of perioperative sympatholysis, the logistics of PBB are influenced by patient risk, the planned surgical procedure, and the specifics of perioperative management (fig. 2). Established clinical guidelines of the ACC/AHA should be used to guide the institution and maintenance of therapy in appropriate patients. Results from several recently launched large-scale trials should ultimately refine our use of this simple but powerful therapy.

References

1. Shojania KG, Duncan BW, McDonald KM, Wachter RM: Safe but sound: Patient safety meets evidence-based medicine. JAMA 2002; 288:508–13

2. Auerbach AD, Goldman L: β-Blockers and reduction of cardiac events in noncardiac surgery: Scientific review. JAMA 2002; 287:1435–44

3. Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE, Fleisher LA, Froehlich JB, Gusberg RJ, Leppo JA, Ryan T, Schlant RC, Winters WL Jr, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Jacobs AK, Hiratzka LF, Russell RO, Smith SC Jr: ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery: Executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Circulation 2002; 105:1257–67

4. Badner NH, Knill RL, Brown JE, Novick TV, Gelb AW: Myocardial infarction after noncardiac surgery. ANESTHESIOLOGY 1998; 88:572–8

5. Kim LJ, Martinez EA, Faraday N, Dorman T, Fleisher LA, Perler BA, Williams GM, Chan D, Pronovost PJ: Cardiac troponin I predicts short-term mortality in vascular surgery patients. Circulation 2002; 106:2366–71

6. Heidland UE, Strauer BE: Left ventricular muscle mass and elevated heart rate are associated with coronary plaque disruption. Circulation 2001; 104: 1477–82

7. Burke AP, Kolodgie FD, Farb A, Weber DK, Malcom GT, Smialek J, Virmani R: Healed plaque ruptures and sudden coronary death: Evidence that subclinical rupture has a role in plaque progression. Circulation 2001; 103:934–40

8. Zaugg M, Schaub MC, Pasch T, Spahn DR: Modulation of beta-adrenergic receptor subtype activities in perioperative medicine: Mechanisms and sites of action. Br J Anaesth 2002; 88:101–23

9. Bristow MR: β-Adrenergic receptor blockade in chronic heart failure. Circulation 2000; 101:558–69

10. Small KM, Wagoner LE, Levin AM, Kardia SL, Liggett SB: Synergistic polymorphisms of β1- and α2C-adrenergic receptors and the risk of congestive heart failure. N Engl J Med 2002; 347:1135–42

11. Zaugg M, Tagliente T, Lucchinetti E, Jacobs E, Krol M, Bodian C, Reich DL, Silverstein JH: Beneficial effects from β-adrenergic blockade in elderly patients undergoing noncardiac surgery. ANESTHESIOLOGY 1999; 91:1674–86

12. Mangano DT, Layug EL, Wallace A, Tateo I: 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

13. Poldermans D, Boersma E, Bax JJ, Thomson IR, van de Ven LL, Blankensteijn JD, Baars HF, Yo TI, Trocino G, Vigna C, Roelandt JR, van Urk H, Fioretti PM, Paelinck B: 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

14. Boersma E, Poldermans D, Bax JJ, Steyerberg EW, Thomson IR, Banga JD, van De Ven LL, van Urk H, Roelandt JR: Predictors of cardiac events after major vascular surgery: Role of clinical characteristics, dobutamine echocardiography, and beta-blocker therapy. JAMA 2001; 285:1865–73

15. Poldermans D, Boersma E, Bax JJ, Thomson IR, Paelinck B, van de Ven LL, Scheffer MG, Trocino G, Vigna C, Baars HF, van Urk H, Roelandt JR: Bisoprolol reduces cardiac death and myocardial infarction in high-risk patients as long as 2 years after successful major vascular surgery. Eur Heart J 2001; 22:1353–8

16. Mukherjee D, Lingam P, Chetcuti S, Grossman PM, Moscucci M, Luciano AE, Eagle KA: Missed opportunities to treat atherosclerosis in patients undergoing peripheral vascular interventions: Insights from the University of Michigan Peripheral Vascular Disease Quality Improvement Initiative (PVD-QI2). Circulation 2002; 106:1909–12

17. Wallace A, Layug B, Tateo I, Li J, Hollenberg M, Browner W, Miller D, Mangano DT: Prophylactic atenolol reduces postoperative myocardial ischemia. McSPI Research Group. ANESTHESIOLOGY 1998; 88:7–17

18. Raby KE, Brull SJ, Timimi F, Akhtar S, Rosenbaum S, Naimi C, Whittemore AD: The effect of heart rate control on myocardial ischemia among high-risk patients after vascular surgery. Anesth Analg 1999; 88:477–82

19. Freemantle N, Cleland J, Young P, Mason J, Harrison J: β Blockade after myocardial infarction: Systematic review and meta regression analysis. BMJ (Clin Res Ed) 1999; 318:1730–7

20. Salpeter SR, Ormiston TM, Salpeter EE: Cardioselective beta-blockers in patients with reactive airway disease: A meta-analysis. Ann Intern Med 2002; 137:715–25