EDITORIALS

Beta-Blocker Therapy in Noncardiac Surgery

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Perioperative myocardial infarction is a major cause of complications and death among patients undergoing noncardiac surgery.[1] Annually in the United States, approximately 27 million patients are given anesthesia for surgical procedures; of these, approximately 50,000 patients have a perioperative myocardial infarction.[2] The pathophysiology of an acute perioperative myocardial infarction is probably the same as it is for infarction unrelated to surgery.[3] In patients with clinically significant coronary-artery stenosis, myocardial ischemia is induced either by a prolonged mismatch between oxygen demand and supply owing to the stress of surgery or as the result of a sudden rupture of a vulnerable plaque followed by thrombus formation and occlusion.

Beta-blockers are commonly used to correct the imbalance between myocardial oxygen demand and supply. In the late 1980s, indications for beta-blocker therapy were hypertension and coronary artery disease, whereas heart failure and peripheral atherosclerotic disease were considered relative contraindications. However, subsequent research has led to the routine use of beta-blockers in patients with stable heart failure. Beta-blockers are also now recommended for patients with peripheral arterial disease who are undergoing vascular surgery.[4]

Despite recommendations by the American Heart Association–American College of Cardiology for the use of beta-blockers in patients with risk factors for coronary artery disease or proven coronary artery disease who are undergoing any type of high-risk surgery (such as intrathoracic or intraperitoneal procedures), evidence of the efficacy of this approach from randomized clinical trials is limited. In a placebo-controlled trial involving 200 high-risk patients, Mangano et al. found that atenolol (50 or 100 mg), administered intravenously beginning 30 minutes before surgery and then orally throughout hospitalization, did not lower the risk of death from cardiac causes or myocardial infarction during hospitalization.[5] However, it did result in a 50 percent reduction in myocardial ischemia, as assessed by continuous 48-hour Holter monitoring. The DECREASE study (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography), involving a high-risk population of 112 patients who were undergoing vascular surgery, showed that the rate of perioperative death from cardiac causes and myocardial infarction among patients who were randomly assigned to bisoprolol therapy (5 or 10 mg) started at least 30 days before surgery was 90 percent lower than that among patients assigned to standard care (3.4 percent vs. 34 percent).[6] In a meta-analysis of six randomized trials involving 694 surgical patients, beta-blockers were associated with a 75 percent reduction in the risk of perioperative death from cardiac causes.[7]

However, not all studies have reported favorable results for beta-blockers. The recently completed DIPOM (Diabetic Postoperative Mortality and Morbidity) trial, involving 921 patients with diabetes who were undergoing noncardiac surgery, failed to show that metoprolol significantly decreased the risk of death and cardiac complications.[8]

In this issue of the *Journal*, Lindenauer et al. report the results of a very large observational study assessing the association between the perioperative use of beta-blockers and in-hospital mortality.[9] The study compared outcomes among 119,632 patients who received beta-blockers during a surgical admission with outcomes among an even greater number of patients who did not receive beta-blockers and who were matched according to the Revised Cardiac Risk Index (RCRI) score. This index stratifies the risk of perioperative cardiac events according to the type of surgery and the presence or absence of a

history of ischemic heart disease, congestive heart failure, cerebrovascular disease, preoperative treatment with insulin, and a preoperative serum creatinine level greater than 2.0 mg per deciliter (176.8 μmol per liter).[10] Scores can range from 0 to 5, and the likelihood of major perioperative complications increases with increasing scores. A patient was considered to have used a beta-blocker if such a medication was prescribed during the first two days after admission. Follow-up was restricted to the period of hospitalization. Overall, beta-blocker use was not associated with a reduced risk of death. However, a steep gradient in the treatment effect was observed in relation to the RCRI score. Beta-blocker use was associated with a 43 percent increase in the risk of death among patients with an RCRI score of 0 and a 13 percent increase among patients with a score of 1; in contrast, it was associated with a reduction in the risk of death (ranging from 10 percent to 43 percent) among patients with a score of 2, 3, or 4 or greater. Thus, beta-blockers appeared to be harmful in low-risk patients, neutral in patients at intermediate risk, and beneficial in high-risk patients.

Previous reports have suggested that the absolute reduction in risk associated with beta-blocker use is most pronounced in patients at high risk for coronary events.[11] However, an interaction between beta-blockers and cardiovascular risk factors, as found by Lindenauer et al., has not previously been observed. In fact, it is hard to explain why beta-blockers would not confer protection in patients with a limited number of risk factors — for example, only a history of ischemic heart disease — but would do so if one or two additional risk factors were present, such as diabetes mellitus or renal dysfunction. As the authors acknowledge, it is possible that the approach they used to identify patients taking beta-blockers was at least partially responsible for this unexpected observation. Beta-blockers may have been given to many low-risk patients in response to a cardiovascular complication, rather than to prevent one. The lack of information in the database on the timing of prescriptions for beta-blockers relative to surgery or on indications for prescribing made it impossible for the authors to address this issue.

How might beta-blockers improve the postoperative outcome among high-risk patients? Beta-blockers prolong coronary diastolic filling time and may prevent fatal ventricular arrhythmias and the rupture of atheromatous plaque in the presence of high sympathetic nervous system drive.[4] These effects may vary with the dose and type of beta-blocker (cardioselective vs. nonselective), as well as with the associated degree of heart-rate control. A small randomized study showed a reduced incidence of myocardial ischemia among patients assigned perioperatively to a regimen that tightly controlled the heart rate (to a maximum of 80 percent of the heart rate at which ischemia had been detected before surgery during ambulatory electrocardiographic monitoring), as compared with those assigned to usual care.[12] Also, all cardiac risk factors may not be equal. For instance, a history of repeated episodes of myocardial ischemia may render the heart more resistant to damage from a prolonged ischemic insult and thus reduce the likelihood or size of a perioperative infarction.[13] Data on such factors are lacking in the study by Lindenauer et al., and therefore beta-blockers may have had differential effects in high-risk as compared with low-risk patients.

The apparent beneficial effect of beta-blockers in high-risk surgical patients in the present study, coupled with earlier reports of such benefits in small randomized trials, supports the routine use of beta-blockers in high-risk patients undergoing noncardiac surgery. Two ongoing randomized trials may help clarify the role of beta-blockers in low-risk or intermediate-risk patients.[14,15] The POISE (Perioperative Ischemic Evaluation) study is designed to evaluate the ability of metoprolol to prevent death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal cardiac arrest in 10,000 patients undergoing all types of noncardiac surgery. DECREASE-IV is designed to evaluate the efficacy of combination therapy with fluvastatin and bisoprolol in 6000 patients scheduled to undergo noncardiac, nonvascular surgery, excluding minor surgery. Pending the availability of data from these trials (expected within four years), we believe it is appropriate to continue beta-blocker therapy in patients at low or intermediate risk, given the potential cardiac risks associated with the sudden interruption of beta-blocker therapy. Further information is needed before the perioperative use of beta-blockers should be considered routinely in other patients at low or intermediate risk.

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Progressive Multifocal Leukoencephalopathy and Natalizumab — Unforeseen Consequences

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In this issue of the *Journal*, there are reports describing in detail three patients in whom progressive multifocal leukoencephalopathy (PML) developed during treatment with natalizumab, a humanized monoclonal antibody against α_4 integrins.[1-3] These patients were among 3000 who had participated in clinical trials of natalizumab for the treatment of multiple sclerosis or Crohn's disease. PML is a deadly opportunistic infection of the central nervous system (CNS) for which there is no specific treatment. It is caused by reactivation of a clinically latent JC polyomavirus infection. This virus infects and destroys oligodendrocytes, leading to multifocal areas of demyelination and associated neurologic dysfunction. The occurrence of PML in this setting was totally unexpected, since it almost invariably occurs in the context of profoundly impaired cell-mediated immunity in patients with AIDS or leukemia or in organ-transplant recipients.

In retrospect, can we retrace the events that led to the surprising development of PML in these three patients? Seropositivity rates for JC virus, the etiologic agent of PML, increase with age and vary in different populations. After infection, the virus remains quiescent in the kidneys and in lymphoid organs of people with immunocompetence. The virus is often present in the urine but is generally not found in the blood. However, JC viremia can be detected in persons with immunosuppression, and hematogenous dissemination is the likely route of entry into the CNS.[4]

Since the authors of the present reports did not provide data on the serologic status of JC virus for the patients, we can only assume that the patients had been infected in childhood. If this is the case, what role did the multiple medications taken by these persons play in the reactivation of JC virus, which eventually led to PML? Retrospective analysis of serum samples that were obtained between 1999 and 2003 from the patient with Crohn's disease provides an important answer: JC virus became detectable only in May 2003, after three injections of natalizumab monotherapy, two months before the patient was admitted to the hospital. Moreover, the serum viral load increased by a factor of 10 after two additional injections.

Therefore, it appears likely that natalizumab, by preventing normal trafficking of lymphocytes, led to unbridled JC virus replication in this patient. Consistent with this scenario, inflammatory infiltrates were conspicuously absent from the brain lesions. Indeed, the cellular immune response, principally mediated by CD8+ cytotoxic T lymphocytes,