The Case for β-Adrenergic Blockade as Prophylaxis Against Perioperative Cardiovascular Morbidity and Mortality

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Perioperative morbidity and mortality are frequently cardiac in origin. Many studies have prospectively attempted to define risk factors for cardiac ischemic events. Although we can now identify high-risk patients, optimal cardioprotective management strategies remain unclear. Treatment with β-adrenergic antagonists decreases myocardial oxygen consumption and is generally well tolerated. This article reviews the physiologic and clinical basis for using these agents as prophylaxis against cardiovascular events in high-risk surgical patients.

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Editor’s Note: This is a thoughtful and timely review of an important issue.

Claude H. Organ, MD

In patients with known cardiovascular disease, myocardial ischemia remains the principal cause of morbidity and mortality after cardiac and noncardiac surgery. As our population ages, this problem will affect nearly 35 million people, with a yearly estimated cost of more than $20 billion. Numerous investigators have prospectively attempted to identify factors that place patients at high risk. A potpourri of historical factors have been implicated, including age, recent myocardial infarction, congestive heart failure, active angina, ventricular dysrhythmias, diabetes, and the type and urgency of the operation. Although we generally can identify patients at high risk for perioperative cardiovascular events, it remains unclear what we should do with this information. No randomized, prospective trial, to our knowledge, has demonstrated the benefit or efficacy of preoperative myocardial revascularization. Indeed, excessive preoperative cardiac screening and subsequent intervention might prove detrimental. The Coronary Artery Revascularization Prophylaxis trial is currently enrolling patients to answer this question. In the meantime, we are left with the dilemma of how best to reduce cardiovascular complications in patients undergoing noncardiac surgery. The purpose of the present article is to review the physiologic and clinical basis for β-adrenergic antagonism in surgical patients.

PHYSIOLOGIC BASIS FOR ADRENERGIC ANTAGONISM

Neurohormonal Stress of Surgery

The neurohormonal stress of elective surgery begins well before the skin incision. Activation of the hypothalamus-pituitary-adrenal axis is initiated by just scheduling the operation and persists throughout surgery until at least a week after surgery. This period, often referred to as the adrenergic-corticoid phase, is defined by hypercatabolism and hypersecretion of neuroendocrine substances. One of the earliest events after afferent stimulation of the hypothalamus is the release of corticotropin and subsequent elaboration of cortisol. Concomitant with adrenal cortical stimulation is medullary activation by the sympathetic nervous system and release of catecholamines. Although the evolutionary intent of these stress reactions is clear in the jungle, these same survival responses, especially if dysregulated, might threaten a debilitated patient with poor reserve. Adrenergic recep-
tors are located in virtually every organ, orchestrating the stress response. In the human heart, $\alpha_1$, $\beta_1$, and $\beta_2$-adrenergic receptors promote several biologic responses, including inotropy, chronotropy, myocyte apoptosis, and direct myocyte toxicity. Left unabated, chronic adrenergic stimulus results in pathologic ventricular remodeling, acute coronary syndromes, arrhythmogenesis, and end-stage cardiomyopathy.

**Myocardial Oxygen Consumption**

Surgery itself obligates myocardial work; patients with coronary artery disease are unable to meet this increased demand. Myocardial ischemia within 48 hours of surgery, either clinically occult or overt, confers a 9-fold increase in risk of unstable angina, nonfatal myocardial infarction, and cardiac death.7 Therapeutic strategies to attenuate this ischemic insult must therefore favorably manipulate the physiologic balance of myocardial oxygen supply and demand.

Myocardial oxygen consumption ultimately reflects the utilization of mitochondrial adenosine triphosphate. As such, conditions that deplete myocardial adenosine triphosphate levels inversely increase oxygen uptake. In 1969, Braunwald8 presented a unified concept of the determinants of myocardial oxygen consumption. Examining nearly a century of experimental studies and a decade of his own work, he elucidated 8 key components—and their relative contributions—of myocardial oxygen consumption. He concluded that the major contributors to cardiac work are heart rate, developed force, and contractile state. In fact, he demonstrated that the catecholamine-induced increase in myocardial oxygen consumption was not so much a function of their direct metabolic effect but rather of their effect on myocardial contractile activity.

Modern interpretation of the thesis by Braunwald8 has focused on 4 prime determinants of oxygen demand: heart rate, preload, afterload, and contractility. Elevated heart rate is associated with shortening of diastolic perfusion (nutrient and oxygen) time. Wall stress (as defined by Laplace’s law) accounts for the contributions of preload and afterload to myocardial oxygen demand. Enhanced contractility affects the equation by changing the relationship between developed pressure and ventricular volume. Cumulatively, a clinical index of myocardial oxygen demand is represented by the “rate-pressure product” (heart rate $\times$ mean arterial pressure). This is one basis for the anesthetic goal of maintaining a patient’s rate-pressure product within 10% of the preoperative value.

**Catecholamines and Myocardial Work**

Catecholamines conspire to increase each of the 4 major determinants of myocardial oxygen consumption. The chronotropic effects of $\beta_2$-receptor stimulation are well recognized. Macrovascular and microvascular tone are, in part, controlled by adrenergic tone. $\alpha_2$-Receptor stimulation promotes venoconstriction, thus affecting afterload and preload. The Figure graphically depicts the relationship among heart rate, blood pressure, and myocardial oxygen consumption (area under respective curves). Compared with the basal state, stimulation with epinephrine increases heart rate (cycles per second), contractility (change in pressure per time), and myocardial oxygen consumption (area integrated under each curve). Compared with the basal state, stimulation with epinephrine increases heart rate (cycles per second), vascular resistance (peak pressure), and contractility (steep slope, ie, an increase in the developed pressure per time). Cumulatively, these catecholamine effects result in an increase in myocardial oxygen consumption.

**CLINICAL BASIS FOR ADRENERGIC ANTAGONISM**

**Early Studies of Perioperative $\beta$-Adrenergic Blockade**

Just as adrenergic stimulation can magnify each determinant of myocardial oxygen demand, adrenergic antagonism can attenuate each variable. Individual studies have associated $\beta$-adrenergic blockade–mediated decreases in myocardial oxygen consumption with a reduction in heart rate, wall tension, and contractility. As a clinical correlate, several studies demonstrate that $\beta$-adrenergic blockade can also decrease perioperative myocardial ischemia.9 Yet, few data—and until recently, no randomized trials—have positively correlated this physiologic effect with clinical outcomes.

The initial study10 demonstrating the beneficial effect of adrenergic antagonism on perioperative morbidity and mortality involved patients with hypertension taking propranolol hydrochloride who seemed to be at risk for propranolol withdrawal syndrome at the time of surgery (Table). Thirteen patients were treated with continuous propranolol infusions after abdominal operations. They strictly monitored serum drug levels, noticed no withdrawal, and reported no perioperative cardiovascular complications. Perioperative propranolol administration subsequently proved to be cardioprotective during cardiac surgery. In another study,11 50 patients undergoing coronary artery bypass surgery were randomized to receive propranolol or placebo 24 to 48 hours before surgery and continuing for 30 days after surgery. Propranolol treatment significantly decreased the rate-pressure product on induction of anesthesia and sternotomy. Cumulatively, patients taking $\beta$-adrenergic
blocking agents had less need for antihypertensive therapy after surgery and experienced reduced incidence and frequency of supraventricular and ventricular arrhythmias and no mortality. Although these studies are small, they suggest the clinical relevance of β-adrenergic blocking agent–dependent decreases in myocardial oxygen consumption as it pertains to myocardial ischemia and possibly arrhythmogenesis.

During the 1990s, several more retrospective and case-controlled studies promoted perioperative β-adrenergic blockade. Stone and colleagues9 gave untreated hypertensive patients undergoing abdominal and vascular surgery a single oral dose of labetalol hydrochloride or atenolol. Whereas 11 of 39 control patients exhibited intraoperative myocardial ischemia, tachycardia and electrocardiographic evidence of ischemia was observed in only 2 of 89 treated patients.8 This study was corroborated in another group of vascular surgery patients given metoprolol, 50 mg, before surgery.12 Compared with controls, treated patients had less frequent and shorter periods of intraoperative silent ischemia.12 These studies did not correlate intraoperative ischemia with cardiovascular outcome. In a retrospective study13 from the University of Oregon, factors associated with perioperative myocardial infarction were analyzed in more than 2000 vascular surgery patients. Use of β-adrenergic blocking agents conferred a 50% reduction in the relative risk of perioperative myocardial infarction. Although this risk reduction is impressive, a surprisingly high number of patients who experienced myocardial infarction were taking β-adrenergic blocking agents (30%). As with the previous studies, outcomes relating the perioperative event to ultimate cardiovascular morbidity and mortality were not reported.

### Randomized Trials of Perioperative β-Adrenergic Blockade

In 1996, Mangano and colleagues14 published the first randomized, prospective trial examining the effect of the cardioselective agent, atenolol, on cardiovascular morbidity and mortality after noncardiac surgery. Two hundred patients at a Veterans Affairs Medical Center undergoing vascular, abdominal, orthopedic, and neurosurgical procedures were randomized to receive placebo (n = 101) or treatment with atenolol (n = 99). Eligible patients were those with previous myocardial infarction, typical angina, or atypical angina with a positive stress test result or those at risk for coronary artery disease (≥2 traditional risk factors). Treated patients received atenolol, 5 to 10 mg, intravenously before surgery and 10 mg, intravenously twice daily or 50 to 100 mg orally until discharge or 7 days maximum. Goals of treatment included a heart rate of 55 to 65 beats per minute (bpm) and systolic blood pressure of less than 100 to 110 mm Hg. The primary end point was all-cause mortality over a 2-year period (99% follow-up); secondary end points included myocardial infarction, congestive heart failure, unstable angina, and myocardial revascularization.

Overall mortality was less in the atenolol vs the control group at 2 years (9% vs 21%). Risk reduction was evident within the first 6 months (no cardiac events in the atenolol group vs 12% in the control group), and the advantage was sustained throughout follow-up. Although the results of this study suggest a role for perioperative atenolol use in providing long-term cardioprotection, these results must be interpreted with several caveats. First, the placebo group suggested a trend toward sicker patients. Second, surgical patients in a Veterans Affairs facility might not be representative of the population at large. Finally, more patients in the treatment group were taking β-adrenergic blocking agents and angiotensin-converting enzyme inhibitors during follow-up. Although atenolol treatment was associated with less perioperative ischemia, β-adrenergic blockade did not significantly reduce the incidence of in-hospital myocardial infarction or cardiac mortality.15 Possibly, the observed decrease in cardiac mortality had nothing to do with the 7 days of atenolol treatment but rather the 6 to 24 months of treatment with other risk-reducing agents.

In 1999, Poldermans and colleagues15 published the second major randomized, controlled trial evaluating perioperative β-adrenergic blockade. This study attempted to define a subgroup of patients who might benefit maximally from adrenergic antagonism. The study by Mangano and colleagues14 reported an extremely low incidence of perioperative cardiac events (3%). This ob-

### Studies of Perioperative β-Adrenergic Blockade*

<table>
<thead>
<tr>
<th>Study, y</th>
<th>Study Type</th>
<th>Patients, No.</th>
<th>Surgery</th>
<th>Drug</th>
<th>Comment†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smulyan et al,10 1982</td>
<td>CC</td>
<td>13</td>
<td>General abdominal</td>
<td>Propranolol</td>
<td>No perioperative cardiac events noted</td>
</tr>
<tr>
<td>Hammont et al,11 1984</td>
<td>PR</td>
<td>50</td>
<td>Coronary artery bypass</td>
<td>Propranolol</td>
<td>Decreased myocardial oxygen demand, infarction, and arrhythmias</td>
</tr>
<tr>
<td>Pasternack et al,12 1989</td>
<td>CC</td>
<td>48</td>
<td>Peripheral vascular</td>
<td>Metoprolol</td>
<td>Decreased silent intraoperative myocardial ischemia</td>
</tr>
<tr>
<td>Yeager et al,13 1995</td>
<td>CC</td>
<td>53</td>
<td>General vascular</td>
<td>NA</td>
<td>Associated with a 50% reduction in perioperative myocardial infarction</td>
</tr>
<tr>
<td>Mangan et al,14 1996</td>
<td>PR</td>
<td>99</td>
<td>Noncardiac</td>
<td>Atenolol</td>
<td>Decreased combined cardiac events from 21% to 10% at 2 y</td>
</tr>
<tr>
<td>Poldermans et al,15 1999</td>
<td>PR</td>
<td>59</td>
<td>Major vascular</td>
<td>Bisoprolol</td>
<td>Decreased combined cardiac events from 34% to 3.4% at 30 d</td>
</tr>
<tr>
<td>Urban et al,16 2000</td>
<td>PR</td>
<td>60</td>
<td>Total knee arthroplasty</td>
<td>Esmolol</td>
<td>Decreased myocardial ischemia; no statistical difference in cardiac events</td>
</tr>
</tbody>
</table>

*CC indicates case controlled; PR, prospective, randomized; and NA not available.
†Cardiac events include perioperative myocardial infarction, congestive heart failure, unstable angina, and death.
CARDIAC events were observed in 34% of the control group compared with only 3.4% of the bisoprolol group. In addition, there were no myocardial infarctions in the treatment arm. These significant differences prompted the safety committee to suspend the trial (original recruitment goal was 266 patients). Although impressive, these results must also be interpreted with several caveats. This was a nonblinded study with fairly low patient numbers. Two groups of patients were excluded from randomization: those already taking β-adrenergic blocking agents and those with extensive wall-motion abnormalities on stress echocardiography. The authors offered no explanation for the 7.5% cardiac mortality rate seen in 53 patients already receiving β-adrenergic blockade. Intuitively, it seems that these patients should also have been protected. Of 8 patients with extensive wall-motion defects (defined by wall-motion index), 4 underwent coronary artery bypass (2 died) and 4 underwent vascular surgery with β-adrenergic blockade (1 perioperative myocardial infarction). Nonrandomization aside, inclusion of these “fringe” patients would not significantly change the overall impact of the study. These patients were clearly sicker and more homogeneous than those in the study by Manganol and colleagues. As such, the conclusion that perioperative β-adrenergic blockade is cardioprotective in high-risk patients undergoing major vascular surgery seems valid.

CONCLUSIONS AND RECOMMENDATIONS

Consistent in the surgical literature is that use of β-adrenergic blocking agents by patients with cardiopulmonary disease is well tolerated. Most patients could achieve the hemodynamic goals of heart rate and systolic blood pressure without developing bronchospasm or congestive heart failure. Although the bisoprolol study excluded patients with asthma, current recommendations do not automatically exclude patients with reactive airway disease from receiving β-adrenergic blocking agents. In fact, judicious titration of cardioselective adrenergic antagonists seems to be indicated in patients with mild to moderately severe asthma and coronary artery disease. Likewise, the historic contraindication of β-adrenergic blockade in patients with reduced left ventricular function and congestive heart failure has been revisited in the past decade. Cardioselective and newer-generation β-adrenergic blocking agents have been successfully used in patients with New York Heart Association class II and III symptoms.

Although therapeutic delivery of adrenergic antagonists is often premised on decreasing catecholamine-induced myocardial oxygen consumption, several other mechanisms likely contribute to their cardioprotective effect. Catecholamines instigate and perpetuate vascular injury by promoting endothelial dysfunction, platelet aggregation, endovascular adhesion molecule release, hypercoagulability, hypertension, and direct myocyte toxicity. β-Adrenergic blockade, experimentally and epidemiologically, can reverse many of these effects. In addition, use of β-adrenergic blocking agents might inhibit apoptosis and platelet deposition, thus stabilizing the vulnerable coronary plaque. Finally, although use of β-adrenergic blocking agents has often been associated with dyslipidemias (particularly reduction in high-density lipoprotein levels), changes in lipid profiles are usually small and outweighed by the cumulative cardioprotective effect of these agents.

There are several different approaches to providing perioperative cardioprotection. Although many of these strategies remain experimental or anecdotal, others have been studied in controlled trials. The former category includes synthetic oxygen carriers, antiplatelet agents, bradykinin antagonists, adenosine, opioid receptor antagonists, and inflammatory mediator antagonists. Traditional perioperative pharmacotherapy has often included calcium channel blockers, nitrates, and α1-adrenoceptor agonists. As with β-adrenergic blocking agents, these agents affect the vasculature and myocardial oxygen consumption at several levels. For example, use of nitroglycerin decreases demand by its venodilatory properties. In addition, nitroglycerin is also a coronary vasodilator and direct nitric oxide donor. Although use of nitroglycerin intuitively makes sense and is supported in several studies, results of a conflicting study suggest that nitroglycerin use has no effect on intraoperative ischemia and might even be deleterious. While we support the use of adrenergic antagonists, it would be naive to suggest that use of these agents, alone, will independently confer protection. β-Adrenergic blockade should be part of a comprehensive pharmacologic strategy that includes other drugs, such as aspirin, angiotensin-converting enzyme inhibitors, and hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins), that reduce the risk of cardiovascular events.

In gratifyingly intuitive fashion, perioperative administration of β-adrenergic blocking agents for the prevention of surgical cardiovascular morbidity and mortality is based on physiologic principles and is supported by randomized, prospective trials. In 1996, the American Heart Association published a consensus statement addressing the preoperative workup and treatment of patients undergoing noncardiac surgery. Subsequently, major studies have reported the beneficial effect of perioperative β-adrenergic blockade on the reduction of cardiovascular events. On review, we therefore offer the
following specific recommendations for patients undergoing major elective noncardiac surgery:

1. Identify patients at high risk: Most of this information can be obtained through the history and physical examination. A 12-lead electrocardiogram and basic laboratory tests to assess anemia, renal function, and glucose tolerance cover most other risk factors. Although it is tempting to obtain a functional study (such as a stress echocardiogram), preoperative myocardial revascularization is currently indicated only in patients who exhibit well-accepted criteria for coronary artery bypass (such as unstable angina).

2. Continue or initiate β-adrenergic blockade: If men older than 40 years and women older than 45 years are already taking a β-adrenergic blocking agent, continue therapy with a goal of lowering heart rate and systolic blood pressure to 70 bpm and 110 mm Hg, respectively. If the patient is not taking a β-adrenergic blocking agent, begin an oral regimen as early as possible preceding the scheduled surgery to achieve the previously stated hemodynamic goals. The optimal β-adrenergic blocking agent remains unclear; however, a cardioselective agent (such as atenolol or metoprolol) is likely the best choice.

3. Continue β-adrenergic blockade throughout hospitalization: In the absence of bradycardia (heart rate <60 bpm) and hypotension (systolic blood pressure <100 mm Hg), judicious use of intravenous and oral β-adrenergic blocking agents should be continued after surgery, with a target heart rate of 70 bpm and systolic blood pressure of 110 mm Hg.

4. Continue β-adrenergic blockade as an outpatient: Although in the study by Poldermans et al13 patients were administered bisoprolol for only 30 days, many cardiologists recommend more prolonged therapy. For reasons that remain unclear, protection against cardiovascular events seems to extend beyond the period of direct adrenergic inhibition.

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REFERENCES


