# Perioperative Beta-Blockade and Late Cardiac Outcomes: A Complementary Hypothesis

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THE PROBLEM OF perioperative cardiac morbidity has been studied for more than a century.[1,2] Now, with approximately one third of the 40 million annual inpatient procedures being performed on patients at risk for coronary artery disease (CAD),[3] estimates are that up to 50,000 patients per year sustain a perioperative myocardial infarction and that, of those, a substantial percentage will die.[4] A variety of pharmacologic interventions have been tested in efforts to limit perioperative cardiac morbidity that is caused by CAD including beta-blocking agents, alpha$_2$-agonists, calcium channel blockers, and nitroglycerin. Of these, beta-blockers have shown the most consistent and well-documented efficacy for decreasing adverse perioperative cardiac events.[5] Although clinicians traditionally consider that effects on myocardial oxygen supply and demand provide the primary benefit of beta-blocking drugs for this patient population, the complexity of the interactions among the sympathetic nervous system (SNS), the heart, and the innate inflammatory immune response may provide other explanations for the benefit of perioperative beta-blockade.

Until the middle of the last decade, most clinical studies of perioperative cardiac morbidity studied early postoperative cardiac events including ischemia, infarction, or heart failure. In 1996, Mangano and colleagues[6] published their results from a carefully conducted randomized clinical trial suggesting that a beta$_1$-adrenergic receptor blocking drug, atenolol, decreased the incidence of fatal cardiac events and improved survival for up to 2 years after surgery. The study population included patients with known or suspected CAD who were scheduled for major surgery under general anesthesia. After randomization, patients received either placebo or atenolol immediately before and for up to 7 postoperative days. For those patients who received atenolol, the length of time between surgery and a first cardiac advent (congestive heart failure, myocardial infarction, unstable angina, cardiac surgery) or death was significantly increased leading to a survival benefit that was not immediately apparent but that evolved over the first 6 to 8 months after surgery. More recently, Poldermans et al[7] published their results from a similar clinical trial that was conducted exclusively in vascular surgical patients who had preoperative evidence of CAD (assessed by stress echocardiography). Patients randomly received either "standard care" or standard care plus the beta$_1$-receptor blocker, bisoprolol, for 30 days after surgery with bisoprolol administration beginning at least 1 week before surgery. During the first 30 days after surgery, 18 patients in the standard care group had a myocardial infarction or cardiac death compared with 2 in the bisoprolol-treated group ($p < 0.001$), suggesting an immediate benefit from perioperative beta$_1$-blockade.[7] However, during long-term follow-up, with bisoprolol continued for up to 30 months, a difference in the incidence of cardiac events (cardiac death, myocardial infarction) between the surviving treated and untreated patients continued to accrue ($p = 0.025$). The decrease in long-term cardiac events for treated patients suggested a treatment effect that was due to the acute perioperative administration of bisoprolol, long-term administration of bisoprolol, or both.[8] The authors note that the long-term benefit of bisoprolol treatment was observed in those subgroups of patients who had either extensive or limited preoperative evidence of stress-induced myocardial ischemia. There are important methodologic differences between these 2 studies,[9] but both suggest that an intervention affecting one or more of the acute physiologic disturbances that are associated with major surgery can lead to delayed and durable benefits for patients with preexisting CAD.

Although neither study assessed the potential mechanism(s) by which perioperative beta-blockade improves long-term cardiac outcomes, both studies based their respective treatment interventions on a background of clinical research that strongly suggests the benefits of beta-blockade are derived from limiting SNS responses to surgery. Limiting the SNS response to surgery, in turn, decreases the incidence of perioperative myocardial ischemia, which clearly correlates with a worsened postoperative survival.[10-12] Although other potential effects of perioperative beta-blockade have been suggested including antiarrhythmic and antirenin effects, augmentation of natriuretic peptide release,[7,8] and the possibility that beta-blockers decrease the heart rate at which patients become ischemic,[11] the most likely beneficial treatment effect of perioperative beta-blockade is generally assumed to derive from the following physiologic relationships (scenario A):

1. Perioperative myocardial ischemia is associated with a worsened long-term cardiac outcome.
2. Perioperative myocardial ischemia is often caused by an imbalance of myocardial oxygen supply and de-

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mand because of SNS activation that causes increased heart rates and myocardial contractility.
3. Beta-adrenergic blocking drugs limit increases in heart rate and myocardial contractility, thereby preventing a perioperative imbalance of myocardial oxygen supply and demand.
4. Therefore, beta-adrenergic blocking drugs improve cardiac outcomes after surgery by preventing SNS-mediated heart rate and contractility responses that cause an imbalance in myocardial oxygen supply and demand.

Do existing data leave room for an alternate, or additional, mechanism to explain the survival benefit of perioperative beta-blockade? Could the remarkable finding of improved postoperative survival rates that evolve over months to years after major surgery be a physiologic consequence of beta-blocker drug effects that are not mediated solely by the myocardial oxygen supply and demand relationship? The authors would like to propose the following alternative explanation and a complementary hypothesis to explain the long-term benefit of perioperative beta-blockade (scenario B):

1. Perioperative myocardial ischemia defines a group of patients who are at risk for a worsened long-term outcome because of late postoperative cardiac events.
2. In the subgroup of patients who manifest perioperative myocardial ischemia, late cardiac events can be, and often are, caused by perioperative activation of the innate inflammatory immune response that, in turn, causes a rapid, but initially subclinical progression of CAD.
3. $\beta_1$-selective blocking agents (such as atenolol and bisoprolol) modify perioperative activation of the innate inflammatory immune response by inhibiting $\beta_1$-mediated proinflammatory events, by promoting a predominance of $\beta_2$ anti-inflammatory events, or by both mechanisms.
4. Therefore, the authors hypothesize that $\beta_1$-blocking drugs improve cardiac outcomes after major noncardiac surgery by attenuating perioperative inflammatory events that cause postoperative progression of CAD, which then leads to late cardiac morbidity.

The complementary hypothesis derived from scenario B implies that there should be data to support the following statements:

1. An exclusive causal link between beta-blocker drug effects on the perioperative myocardial oxygen supply/demand relationship and late cardiac events is arguable based on existing evidence.
2. Transient physiologic events that are restricted in time (the perioperative period) can measurably affect the progression of CAD. In other words, the progression of CAD is a phasic or episodic event rather than a slow, continuous event.
3. The innate inflammatory immune response to surgery includes activation of chemical and/or cellular mediators that are involved in the phasic progression of CAD.
4. $\beta_1$ antagonists and/or $\beta_2$ agonists can limit the activation of those components of innate inflammatory responses that are involved in the phasic progression of CAD.

The authors now look briefly at each statement.

An exclusive causal link between beta-blocker drug effects on the perioperative myocardial oxygen supply/demand relationship and late cardiac events is arguable: several lines of evidence lend support to this statement. First, the reported differences in heart rates between beta-blocker–treated and –untreated surgical patients are usually small. Further analysis of data from the study by Mangano et al[11] showed that the mean postoperative heart rate in the atenolol-treated group was 75 beats/min, whereas in the control group it was 87 beats/min. Although it is important to note that averaging obviously obscures individual heart rate events that may cause perioperative myocardial ischemia, similar differences were reported by Poldermans et al[7] as well as by other investigators.[13] Second, other anti-ischemic interventions (nitroglycerin and calcium channel blockers) that should prevent an imbalance in myocardial oxygen supply and demand have not shown the same kinds of benefits for surgical patients at risk.[5,14,15] Third, the safety of chemically induced increases in myocardial oxygen consumption (catecholamines and anticholinergics) during stress echocardiography has been documented by many centers in which thousands of individual tests have been conducted with substantial increases in myocardial oxygen consumption and no or very little evidence of adverse long-term effects.[16] Finally, and perhaps most convincingly, there are data from many large trials to suggest that a deliberate *increase* in perioperative cardiac performance does not worsen cardiac outcomes or survival rates and, in fact, may improve survival rates.[17-24] The primary hypothesis in these studies has been that a deliberate increase in perioperative cardiac output, which necessitates increases in heart rate and stroke volume, will improve postsurgical survival. Using either a $\beta_2$-selective agonist (dopexamine) or a mixed $\beta_1$ and $\beta_2$ agonist (dopamine or adrenaline), these studies have shown that an increase in perioperative cardiac performance leads to improved surgical survival or to no measurable benefit, but in none was it shown to worsen postoperative outcome or survival. The patients enrolled in these studies, most of whom would be considered as "at risk" for CAD, typically experienced increases in perioperative heart rates rather than the decreases in heart rate reported from perioperative beta-blocker trials.[17,20,21] Although the results from these studies of "supranormal" perioperative cardiac performance have been inconclusive, they further show that a direct causal link between perioperative increases in myocardial oxygen consumption and adverse long-term cardiac outcomes is a difficult connection to make, leaving room for an alternative explanation for beta-blocker–mediated improvements in postoperative survival.

Progression of CAD is a phasic or episodic event: if the transient physiologic disturbances that accompany major surgery are able to affect cardiac events that manifest months to years later, there should be evidence to show that the progression of coronary artery disease can be an episodic or intermittent event. The traditional view held that CAD symptoms were the end result of a slow, progressive narrowing in coronary arteries that continued until the narrowing reached a critical threshold that then led to ischemic myocardial symptoms