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Beta blockade: The right time, the right dose, the right receptor!

Ahmed M. Al-Mousawi, MB BS, MRCS, Marc G. Jeschke, MD, PhD, and David N. Herndon, MD, FCCM

The University of Texas Medical Branch, Shriners Hospitals for Children Galveston, TX

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In this issue of *Critical Care Medicine*, Ackland and colleagues (1) report findings from a series of experiments, using β blockade in rodent models of endotoxic shock and sepsis. Experiments included daily intraperitoneal injections of metoprolol and atenolol, both selective β_1 -adrenoceptor antagonists, commencing 2 days before or 6 hrs after induction of endotoxemia, using lipopolysaccharide. The authors demonstrated a significant survival advantage when either agent was given before, but not after, lipopolysaccharide administration. Not only was the survival benefit remarkable but they also found that, when administered with adequate fluid resuscitation at a dose to reduce heart rate by 20%, the agents did not cause hypotension, maintaining both cardiac output and blood pressure. Metoprolol pretreatment was also associated with lower interleukin-6 as well as reduced production of various inflammatory cytokines in hepatic and cardiac tissue.

Perioperative risk reduction with β blockade use has remained a controversial issue despite a number of large clinical trials. In a single center trial by Mangano et al (2) that was conducted at a veteran affairs medical center, 200 patients were enrolled and determined to be at risk of coronary artery disease according to at least two risk factors. A fixed dose of atenolol was commenced immediately before noncardiac elective surgery, and continued for up to 7 days during hospital stay. A significant reduction in cardiac-related mortality was reported, primarily over the first 6 to 8 mos, although mortality remained 15% lower at 2 yrs. Poldermans and colleagues (3) later reported in a landmark study that β blockade reduced mortality and myocardial infarction in high-risk patients undergoing vascular surgery, suggesting potential benefits of β blockade in adult and elderly patients undergoing surgery.

The perioperative ischemic evaluation (POISE) trial (4), the largest study to date to address the issue, reported results from an international, multicentered trial that enrolled 8351 patients aged >45 yrs (mean age = 69 yrs), before undergoing noncardiac surgery. Metoprolol was reported to reduce cardiovascular deaths, nonfatal myocardial infarction, or nonfatal cardiac arrest (combined reduction from 6.9% to 5.8%), but was found to increase the risk of both stroke (increased from 0.5% to 1.0%) and overall mortality (increased from 2.3% to 3.1%) at 30 days. Clinically significant hypotension and bradycardia were considerably higher in the metoprolol group, although checked before administration and doses adjusted if required. Criticisms of the study included the high occurrence of

hypotension, patient selection, dosing regimen and lack of titration, and use of a long-acting controlled release formulation of metoprolol (5) that would preclude adjustment.

Our group has investigated β blockade post severe burns, finding strong evidence for a reduction in morbidity and mortality. Herndon et al reported that postburn administration of propranolol, a nonselective β receptor antagonist, exerts strong anticatabolic effects and attenuates the hypermetabolic response (6). Propranolol was given post admission and titrated to decrease heart rate by 15% to 20%. The hypermetabolic response post severe burns is mediated by increased production of catecholamines (7) and induces a catabolic state that persists for about 2 yrs post injury (8, 9). Similar to other forms of severe trauma, catecholamines lead to major increases in metabolic rate, heart rate, and cardiac work as well as peripheral lipolysis and loss of lean body mass (7, 10, 11). In addition to improving metabolic alterations post burn, propranolol has been found to reduce safely cardiac work by decreasing heart rate and to improve cardiac filling and stroke volume (12, 13). However, these findings need confirmation in a multicenter trial. It is also interesting that propranolol exerts these effects despite being a nonselective antagonist. We speculate that propranolol may also exert effects on α_1 receptors, although this remains to be determined.

What evidence-based guidelines are currently available? The first guidelines to address cardiac risk reduction and perioperative management in patients undergoing noncardiac surgery have just been published by the European Society of Cardiology (14). These include recommendations that a combination, rather than a single agent, is most likely to prove of benefit for perioperative risk reduction. Pharmacologic interventions to be considered include β blockers, statins, aspirin, and angiotensin converting enzyme inhibitors. They recommend commencing or continuing a low-dose β blocker in patients with known risk factors or in patients undergoing intermediate to high-risk surgery. Doses of β blockers should be titrated, implying therefore that treatment should ideally be started between 30 days to at least 1 wk before surgery, with titration to achieve a heart rate between 60 beat/min and 70 beat/min and a systolic blood pressure >100 mm Hg before surgery. The guidelines recommend the use of selective β_1 -adrenoceptor blockers bisoprolol (2.5 mg daily) or metoprolol succinate (50 mg daily), long-acting agents without intrinsic sympathomimetic activity. Postoperative complications should be addressed as a cause of tachycardia before considering dose adjustment. Aspirin should be continued unless hemostasis during surgery may be difficult, and preoperative coronary interventions should also be discussed as the associated post procedure antiplatelet therapy (aspirin or clopidogrel) may also affect management. The optimal duration of treatment remains unresolved at present from the currently available evidence.

Results from the Dutch Echographic Cardiac Risk Evaluation Applying Stress Echo (DECREASE) III trial have just been published (15) on perioperative events in patients, >40 yrs of age, undergoing non-cardiac vascular surgery. Patients were found to benefit from the addition of a statin (fluvastatin, 80 mg daily) to a β blocker, commencing at a median of 37 days before surgery. Both statin and control patients not already on a β blocker commenced a titrated dose of bisoprolol (2.5 mg daily) on initial visit. Key findings for statin-treated patients compared with controls included lower postoperative myocardial ischemia within 30 days of surgery (10.8% vs. 19.0%), a primary end point, and significantly fewer deaths from cardiac causes (reduced from 10.1% to 4.8%), although the study was not powered for this secondary end point. Total and low-density lipoprotein cholesterol and inflammatory markers were also reduced by the time of surgery. Patients benefited from a statin despite normal cholesterol levels.

To summarize, it is presently not entirely clear when and in whom to use β blockade, which receptor to target, to use selective or nonselective agents, at what dose, and for how long to

continue therapy. The current study by Dr. Ackland and colleagues (1) adds to the growing evidence that β_1 blockade may improve survival in septic and critically ill surgical patients. To resolve these questions requires well-designed, strict, and specific clinical protocols. In designing such protocols, we will hopefully avoid errors that have been made in the past with other agents, and most importantly, we will determine how to improve outcomes for various patient populations. We would like to end this editorial with the following suggestion: It is not only β_1 blockade, it is a matter of the right receptor, the right time, and right dose.

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