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Challenges of β-Blockade in Surgical Patients

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THE paper by Wallace *et al.*[1] in this issue of ANESTHESIOLOGY offers an important contribution to a field that has recently been through a very stormy period.

In the early 1970s, it was recognized that β-blockade was compatible with anesthesia and offered the advantage of hemodynamic stability at the time of sympathetic stimulation—in addition to reducing the risk of myocardial ischemia and ventricular arrhythmias.[2] This reduction of the risk of perioperative myocardial ischemia,[3,4] arrhythmias, and myocardial infarction[5] was confirmed in later studies.

A decade later, two randomized controlled trials showed improved survival with perioperative β-blockade[6] as well as reduced risk of death and myocardial infarction in the short- and long-term,[7,8] and also reduced incidence of silent myocardial ischemia.[9] Data from both studies were reported, in part, in two papers. Both studies have limitations in their applicability to general noncardiac surgical populations, however; one was a subset of patients from a cohort of 1,350 patients that enrolled only those with reversible ischemia,[7] and the other had a high incidence of diabetes mellitus in the control group. In addition, some patients had their β-blocker stopped before randomization, and in-hospital deaths were ignored in the analysis.[6]

Based on the available evidence, the American College of Physicians[9] in 1996, followed by the American College of Cardiology and the American Heart Association[10] in 1997, recommended β-blockers before noncardiac surgery in all patients with overt coronary artery disease or risk factors for it.[10,11] Indeed, it appeared to some authors that perioperative β-blockade was one of the practices that most improved patient safety.[12]

A number of randomized controlled trials were carried out, some with positive and some with equivocal results.[6,7,13–18] Meta-analyses based on a small number of studies confirmed the efficacy of β-blockade in the prevention of perioperative cardiac complications,[19,20] but those that included a much larger number of studies in noncardiac[21] in addition to combined cardiac and noncardiac surgery[22] found no statistically significant benefits. Over time, guidelines insisted on the need to consider β-blockers in patients at risk (*i.e.*, high-risk surgery, high risk of coronary artery disease) rather than all patients at risk for coronary artery disease. A more cautious approach was recommended.[23,24]

Then came the thunderbolt. It appeared in the form of the PeriOperative ISchemic Evaluation (POISE) Trial.[25] The trial's data showed that perioperative β-blockade significantly reduced the incidence of cardiac events—but at the price of *increased* risk of all-cause mortality and major strokes. Not surprisingly, the study attracted a large number of comments in respect of the choice and dose of β-blocker, the time treatment was initiated, and the heart rate and blood pressure thresholds for the administration of the next dose of the β-blocker.[26–28]

The POISE findings were echoed in meta-analysis by Bangalore *et al.*,[29] such that the case for perioperative β-blockade was suspect.[29] Preliminary analysis of the POISE data suggested that arterial hypotension was an important correlate of stroke and all-cause death.[25] However, a factor not investigated in POISE—or other studies to date—may have been the presence of preexisting anemia, including that due to acute blood loss. Indeed, experimental and clinical data have shown that β-blockade has important detrimental effects on the brain in the presence of anemia.[30,31] During the perioperative period, the current trend for accepting a lower hemoglobin concentration as threshold for blood transfusion may play a role in the development of adverse cerebral events in the face of β-blockade.

Two sets of guidelines were published in November 2009, one on behalf of the American College of Cardiology Foundation and the American Heart Association,[32] the other on behalf of the European Society of Cardiology.[33] Both

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contain recommendations on the perioperative use of β-blockers. Both advocate starting treatment at least 1 week (preferably 30 days) before surgery and adjusting the effects to appropriate heart rates and blood pressures. They also both advocate maintaining β-blockade in patients already on this medication. Both sets of guidelines were prepared before the positive results of the most recent randomized controlled trial—The Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study, DECREASE IV—were published.[34] Because these two sets of guidelines differ, the American College of Cardiology Foundation/American College of Cardiology recommendations being generally more restrictive than those of the European Society of Cardiology, the paper by Wallace *et al.*[1] is timely.

Although randomized controlled trials may be the best evidence there is, they unavoidably contain a built-in degree of artificiality with their inclusion/exclusion criteria and strict protocols for drug administration. Such restrictions make "real-world" epidemiologic analysis particularly important. Yet, even these studies, undoubtedly, have their limitations. In the case of Wallace *et al.*,[1] the data were collected in a department known for its interest in myocardial ischemia and cardiac protection. The study was a natural extension of earlier work to develop a program for perioperative β-blockade: the Perioperative Cardiac Risk Reduction Therapy Protocol, PCRRT. Patients were considered for inclusion if they had proven coronary artery disease, previous or current vascular surgery, or two of the following risk factors: diabetes mellitus, hypertension, age older than 60 yr, smoking, or hyperlipidemia. Such inclusion criteria are very similar to those of POISE, but completely different from DECREASE,[7] because the latter study included only patients with reversible ischemia on a stress test.

Further, the data presented by Wallace *et al.*[1] include 38,779 operations over 12 yr and reveal an almost equal number of operations in patients taking (52%) *versus* not taking (48%) a β-blocker. Over a 1-yr period, survival rates were equal in those who were started on a β-blocker at the time of surgery and those in whom this therapeutic regimen was continued. This holds true for all types of surgeries, though the data may show only trends in the case of relatively small subgroups. This is important information because cardiac protection by long-term β-blockade has not been universally reported,[35] possibly because β-blockade in previous studies was either not reliably given during surgical admission or the dose was inadequate to ensure cardiac protection. The study of Wallace *et al.*[1] therefore supports the accepted policy of maintaining treatment with β-blockers throughout the perioperative period, a policy based hitherto on relatively limited evidence.[36,37] At 30 days and 1 yr the benefits of maintaining β-blockade were seen in the higher risk patients (*i.e.*, class 2–6 per Revised Cardiac Risk Index[38]) and in all types of surgeries. Maintenance of β-blockade must be associated with appropriate dosing protocols to avoid hypotension, which was an important determinant of adverse outcomes in POISE.[25] The importance of maintaining β-blocker therapy in patients undergoing noncardiac surgery has also been emphasized by the recent observational study of van Klei *et al.*[39] in orthopedic surgical patients.

When considering the benefits *versus* risks of β-blockade, interactions between β-blockade and other concurrent therapies and comorbidities need to be evaluated. In many recent studies of perioperative β-blockade, the continued administration of concomitant cardiovascular drugs is often not specified. This factor may be especially relevant in the case of statins, because their continuation is known to be beneficial and their withdrawal is associated with increased morbidity.[40] During studies of long duration, it is likely that an increasingly large proportion of patients received statins. Wallace *et al.*[1] introduced clonidine in their protocol, an addition that may, therefore, have played a role in the degree of protection offered by the initiation of β-blockade.

What the study by Wallace *et al.*[1] also shows is that absence of β-blockade—either through nonadministration as a result of clinician's choice or active drug withdrawal—is associated with reduced survival. The study confirms that β-blockade withdrawal is associated with significantly worse outcomes even in the lowest risk patients.

The recent guidelines insist on starting β-blockade at least 1 week before surgery.[32,33] This was not the case with the PCRRT protocol; β-blockade, when added at the time of surgery, was started the day of surgery. This was the case for 5,832 operations. However, the addition of a β-blocker in this manner proved better than no β-blockade. The concept of starting β-blockade long before surgery is logical, but not always practical. Moreover, very few randomized controlled trials have used this approach,[7,34,41] including, to a limited but unspecified extent, the Perioperative β-Blockade or POBBLE study.[15] The total number of patients is only 662 in all these studies. This is in contrast to the 6,474 patients who received a β-blocker immediately before surgery as reported in the meta-analysis by Bangalore *et al.*[29]—and now the 5,832 operations reported by Wallace *et al.*[1] in this issue of the Journal. The evidence for starting β-blockade several weeks before surgery is, therefore, not firmly established. Not surprisingly, over the 12 yr of the Wallace *et al.* study, there was an increase in the proportion of patients who continued with β-blockers and a decrease in those who did not receive them.

What are the messages of the paper by Wallace *et al.*? What should the clinician do now? As for any treatment, β-blockade has to be considered from a risk/benefit perspective. With or without studies, it stands to reason that at-risk patients are likely to benefit more, as was shown by Lindenauer *et al.*[42] in the largest observational cohort of β-blockade in surgical patients ever published. The Wallace *et al.*[1] data show that the addition or continuation of β-blockade reduced mortality in higher risk patients. As with all potent agents, there is need for protocols that address initiation and administration of successive doses, especially in the face of the hemodynamic instability that characterizes major surgery and recovery. The current European Society of Cardiology

guideline suggests that 100 mmHg systolic arterial pressure is sufficient for the next dose to be given, whereas American College of Cardiology Foundation/American College of Cardiology guideline indicates that the next dose should be given *in the absence of hypotension*. Wallace *et al.*,[1] in their protocol, required a systolic arterial pressure of more than 120 mmHg. Although either 100 or 120 mmHg may be appropriate in most patients, this threshold may not be sufficient in the case of patients with hypertensive heart disease. We believe that, in these circumstances, any protocols will need to be adjusted to reflect the likely changes in autoregulatory mechanisms.

In view of the current controversies, the Wallace *et al.*[1] study has the merit of confirming in a large cohort that withdrawal of β-blockade is dangerous; conversely, maintenance of β-blockade or its initiation at the time of surgery confers cardiovascular protection; and the absence of β-blockade in at-risk patients increases the risk of adverse cardiac events.

Thus, the case for perioperative β-blockade in noncardiac surgical patients, as questioned by the findings of POISE, has been partially reestablished. What is needed now are more studies answering the issues of when is best to start treatment and for how long; whether one class of β-blockers has greater risk-benefit advantage; which route of perioperative administration is preferable[43]; and, most importantly, how best to maintain careful monitoring of these patients in the preoperative, perioperative, and postoperative periods with active treatment of any adverse effects. In this way, the cardioprotective utility of an important class of drugs in the perioperative period is likely to be enhanced.

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