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Perioperative Use of β-Adrenergic Antagonists and Anemia

Known Knowns, Known Unknowns, Unknown Unknowns; and Unknown Knowns

IN seminal publications, Mangano *et al.* demonstrated an association of postoperative tachycardia and myocardial ischemia in patients with or at risk for coronary artery disease, after surgery other than cardiac surgery,[1] after having previously shown an association between postoperative ischemia and adverse cardiac outcomes.[2] Thus, a link was established for postoperative tachycardia, myocardial ischemia, and adverse outcomes. That group followed with a logical extension of their work, showing in a prospective, randomized, double-blinded, but relatively small trial of 200 patients, with or at risk for arteriosclerotic coronary artery disease, undergoing surgery other than cardiac surgery, that administration of a β-adrenergic antagonist begun immediately before surgery and continued for the first of 7 days or hospital discharge decreased postoperative myocardial ischemia,[3] and long-term (2-yr) mortality.[4] The former publication was accompanied by an editorial by Warltier,[5] decrying the underutilization of β-adrenergic antagonists.

These results were confirmed by another small (112 patients) prospective, randomized, but not blinded, trial in patients with dobutamine echo–confirmed coronary arteriosclerotic heart disease in which another β-adrenergic antagonist, bisoprolol, initiated at least 1 week before surgery, and continued until postoperative day 30, decreased cardiac and all-cause mortality and nonfatal myocardial infarction.[6] The results of these trials and several endorsements and recommendations led to wide-spread acceptance and use of this class of drugs in patients at high risk for myocardial ischemia and by some clinicians for patients with lesser risk, as well. Perhaps, acceptance and use were facilitated by the sound physiologic and pathophysiologic basis for these findings: that β-adrenergic antagonism (even if partial) decreases myocardial oxygen consumption by decreasing heart rate (and, thus, work) and myocardial contractility, while at the same time increasing diastolic time and coronary artery flow, thus improving the balance of myocardial oxygen delivery and oxygen consumption. Also, it has been speculated that at least some of the β-adrenergic blockade–induced reduction of myocardial infarction may be due to plaque stabilization,[7] because of hemodynamic-induced plaque stress reduction.

More recently, a flawed retrospective analysis using propensity score, but with unsuccessful matching, of more than half a million surgical patients in 329 U.S. hospitals noted a decreased mortality for high-risk patients but no improvement of mortality for low-risk patients given β-adrenergic antagonists during the first 2 days of hospitalization. Notably, the date of surgery was unknown.[8] Subsequently, some clinical trials have failed to reproduce these previous results. However, one was underpowered to detect a decrease of even 50% of cardiac events,[9] and another[10] was halted early because of poor patient recruitment and, thus, also was underpowered.

Complicating the issue further, a randomized prospective trial of 8,351 patients with or at risk for arteriosclerotic disease undergoing noncardiac surgery (41.5% had vascular surgery) in 190 hospitals in 23 countries, taking 5 yr to complete (The PeriOperative ISchemic Evaluation trial) and using a high dose of extended release metoprolol found a benefit of β-adrenergic antagonist administration for a composite cardiac endpoint (cardiovascular death, nonfatal myocardial infarction, and nonfatal cardiac arrest) and all myocardial infarctions, but a greater incidence of death (3.1% *vs.* 2.3%) and stroke (1.0% *vs.* 0.5%); nearly all of the latter was ischemic in origin.[11] This trial, too, was stopped early for the unusual reason, "mainly because the remaining study drug expired" the following month.[11]

A more recent case-controlled examination of a single-center database of 186,779 patients with a much smaller incidence of postoperative stroke (<0.02% when excluding patients who had intracerebral or carotid surgery) failed to find an increased association of computed tomography–confirmed postoperative stroke with chronic β-adrenergic antagonist therapy.[12]

It is difficult to compare these studies as they involved different β-adrenergic antagonists, initiated and administered over varying durations relative to surgery, with popu-

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lations of differing cardiac risk, from different countries with differing standards of care (sometimes within a single report) and with differing inclusion and exclusion criteria (*e.g.*, whether patients had been taking β-adrenergic antagonists before surgery). Some studies had no knowledge of patient medications before surgery. Furthermore, in most prospective trials, it was possible that patients in the placebo group were given β-adrenergic antagonists by their clinician.[6,9,10,13]; these events were not detailed and were ignored in the statistical analyses, as the results were reported for intention-to-treat analyses. Performing such an analysis has certain theoretical and practical advantages, but it is clearly confounded when some of the group not intended to receive the test therapy, in fact, did. In addition, and importantly, all these studies used but a single dose regimen of drug. Virtually all medications have benefits and risks that vary with dose. That is the purpose of a phase II trial: to select the dose that has the best benefit to risk profile. All of these studies lacked that knowledge for the populations studied, and it is entirely possible because of the factors listed earlier that different studies were examining dose regimens with different benefit–risk ratio in differing populations.

In this issue of ANESTHESIOLOGY, *Beattie et al.*[14] add information gleaned from a retrospective analysis of 4,377 patients (90% of whom were at low cardiac risk with a revised cardiac risk index of 0 or 1) undergoing noncardiac surgery (>70% for cancer) at a major teaching tertiary care center. For the 827 of the 1,153 patients who were given any β-adrenergic antagonist of any dose within the first 24 h after surgery and matched using propensity scores for many covariates, they noted an *increased* incidence of their adverse composite cardiac endpoint of myocardial infarction, mortality, and nonfatal cardiac arrest. Although the use of composite endpoints is somewhat controversial,[15,16] this endpoint was driven by myocardial infarction (defined solely as a troponin value >0.7 μg/ml), as the frequency of other events was too low to provide a statistical impact. Importantly, as noted by the authors, this was not a prospective trial, and the very act of ordering a test for troponin (not mandated, but ordered according to clinician desires) confounded the results: that is, the unknown rationale for a measurement had a huge confounding inappropriate[17] effect on the primary endpoint. When, commendably, the authors attempted to reduce this bias with an additional analysis, the probability shifted two orders of magnitude, approaching statistical nonsignificance. In addition, although the two individual high-risk surgical conditions did not differ statistically between matched groups, when combined (as could have been done in the model to define high-risk surgery), the groups given β-adrenergic antagonists had a significantly greater ($P < 0.02$) incidence of high-risk surgery. This likely influenced the result of the primary endpoint. Further understanding is complicated by not knowing dose(s), the number of doses or duration or therapy, or the rationale for their administration. Propensity scoring can reduce bias by matching groups for many covariates. However, it cannot infer or control for intent of clinicians who treated the patients. We do not know whether a β-adrenergic antagonist was administered to treat a transient postoperative increase of heart rate or blood pressure, for an observed ischemic event, for perceived risk, or as a continuation of preadmission/preoperative therapy. Physicians at the authors' institution would likely have selected preoperatively those with the most severe disease for such therapy and have continued it postoperatively as a matter of course, knowing that acute withdrawal is associated with adverse cardiac events.[18,19] Propensity scores can reduce bias based on the disease codes (as was done in this case), but in general not on their severity as these codes do not quantify the severity of the disease process.

Can we make sense of these apparently conflicting results and gain an understanding of what we know? Published studies seem to support the thesis that β-adrenergic antagonists are of benefit for those with proven or at high risk for coronary artery disease but quite likely have a lesser or reversed benefit–risk ratio for others.

State of knowledge has been parsed as "known knowns" (things we know that we know), "known unknowns" (things that we now know we do not know), and "unknown unknowns" (things we do not know we do not know).[20] Beattie *et al.* provided an important service. Propensity scoring is a sophisticated statistical method to reduce bias, but as the authors acknowledge, cause and effect cannot be attributed. However, their publication highlights what is extant in all the above studies and to which I will refer as an "unknown known": that is, ignoring a factor that is known to be of substantial influence. This has been described by Yankelovich[21] as "blindness." Most, but not[2,3,9,22] all, of the above reports treat the period of anesthesia, that of greatest physiologic trespass and pharmacologic prophylaxis and therapy, as a black box (compare with a commercial aircraft's data recorder that is never retrieved and evaluated). None of the previous reports have provided information about the critical issue of hemoglobin concentration, despite the knowledge that severe anemia[23] and preoperative anemia[24,25] are associated with increased mortality. Hence, these reports treated hemoglobin concentration as an "unknown known."

In conscious humans, anemia is compensated by increases in heart rate and stroke volume.[26] The heart rate increase is difficult to ablate even with very high doses of a β-adrenergic antagonist, decreasing stroke volume and cardiac output to a greater extent.[27] We were unable to reduce isovolemic anemia-induced heart rate increases to values obtained before production of isovolemic anemia in conscious healthy humans, despite very high infusion rates of esmolol.[27] The brain lives on the edge of hypoxia (John W. Severinghaus, M.D., oral communication, c. 1970). Isovolemic anemia in healthy conscious humans, at hemoglobin concentrations less than 7 g/dl, delays cerebral signal processing[28] and impairs neurocognitive function,[29–31] suggesting that at this degree of anemia oxygen delivery to the brain is inadequate.

Perhaps, the most important aspect of the report by Beattie *et al.* is that when analyzing their outcome data as a function of decrease in hemoglobin concentration, their ret-

rospective analysis found a relationship between this and their adverse composite outcome. It is unclear whether this represents a surrogate for blood loss (and the possibility of inadequate replacement) or the physiologic effects of anemia.

The PeriOperative ISchemic Evaluation trial[11] treated hemoglobin concentration as an "unknown known"; Beattie *et al.* now appropriately removed hemoglobin concentration from that category. We cannot yet claim that we know the influence of hemoglobin in the cardiovascular and cerebrovascular events when β-adrenergic antagonism is instituted before surgery, but Beattie *et al.* give us a pathophysiologically plausible hypothesis. As they indicated, a prospective randomized trial is required to provide definitive cause and effect. When the nadir hemoglobin concentration was less than or equal to 7 g/dl, the adverse composite outcome increased in both groups (approximately doubled in the control group and approximately tripled in the treated group) and the difference between the groups increased substantially (W. Scott Beattie, M.D., Ph.D., personal communication, September 2009). This would seem to support absolute hemoglobin value as an important independent variable and seems to be in accord with the data regarding the point at which isovolemic anemia affects central nervous system processing and neurocognitive function on the basis of inadequate oxygen delivery,[28–31] and could help explain the stroke data of the PeriOperative ISchemic Evaluation trial.

However, it will be a difficult prospect to perform a prospective randomized clinical trial to test the hypothesis generated by the retrospective analysis by Beattie *et al.* by randomly allocating patients with high risk for, or proven, coronary artery disease to a hemoglobin concentration of 6 g/dl or a value greater than 9 g/dl. Perhaps, the retrospective data analysis by Beattie *et al.* is the best that we will have, absent a *post hoc* analyses of previously conducted randomized trials (the PeriOperative ISchemic Evaluation trial is likely the only one with the possibility of sufficient power for this assessment). Some value retrospective analyses of large databases because of their sample size and the possibility of examining pharmaceuticals as they are used in practice, rather than as dictated by investigational protocols. However, the report by Beattie *et al.* represents the place where a retrospective analysis of a dataset provides its best contribution: when a clinical trial cannot be conducted. Until better data are available, although β-adrenergic antagonists seem to protect the myocardium of high-risk patients and may well be of lesser or no efficacy for patients at lesser risk, it would seem prudent to avoid those agents that substantially impair the cardiac response to acute severe anemia when that or substantial hemorrhage is anticipated.

Richard B. Weiskopf, M.D., Department of Anesthesia and Perioperative Care, University of California, San Francisco, California. rbw@itsa.ucsf.edu

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