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Perioperative β-Blockade, Discontinuation, and Complications

Do You Really Know It When You See It?

CME This article has been selected for the ANESTHESIOLOGY CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

ATTEMPTING to articulate his thoughts on the legal definition of obscenity in the 1960s, Supreme Court Justice Potter Stewart, opined "I know it when I see it."* This approach, celebrated at that time as intuitive and pragmatic, was one he later recanted. Clinicians take a similar approach to situations that are often more complex than they appear. In this issue of ANESTHESIOLOGY, van Klei *et al.* report an analysis of patterns of perioperative β-blocker prescription in patients undergoing orthopedic surgery.[1] They conclude that their results provide confirmatory evidence to one of the two class 1 recommendations for "perioperative β-blockade" of the American College of Cardiology/American Heart Association Perioperative Evaluation Guidelines Committee, paraphrased by the authors as "not to withdraw β-blocker therapy."[2]† As the current guideline comprise only a single paragraph with three literature citations, a closer look at this issue appears timely.

Problems related to perioperative administration of β-blockers have been debated for over 40 yr.[3] In 1972, Viljoen *et al.* set a decidedly negative tone by reporting on five patients undergoing myocardial revascularization at the Cleveland Clinic with "frustrating therapeutic problems" who developed "unexplained intraoperative cardiac failure" attributed "in part to residual propranolol induced myocardial depression," recommending their discontinuation 2 weeks before surgery.[4] In 1975, the hazards of propranolol withdrawal were reported in the *New England Journal of Medicine* in a double-blind crossover efficacy trial in which 10 of 20 patients with angina sustained ischemic complications off therapy.[5] Subsequently, Kaplan *et al.* reported observational data (including the first noncardiac surgery cohort) and Slogoff and Keats, a randomized trial, suggesting that continuation to within 12–24 h of surgery was safe, although neither specifically address postoperative use.[6–8] In fact, β-blockers were often discontinued permanently shortly after myocardial revascularization because it was felt that patients would no longer need them.[9]

In 1981, several years after his landmark Cardiac Risk Index study, Lee Goldman reported case vignettes of (only) two patients with known ischemic disease on chronic propranolol therapy undergoing vascular surgery, outlining the potential hazards of perioperative withdrawal.[10,11] Both patients developed tachycardia and signs of myocardial ischemia early postoperatively, one with overt hemorrhage and evidence of heart failure. Both responded eventually to reinstitution of propranolol. He speculated the cases were "definitive" or "suggestive" of propranolol withdrawal, recommending continuation of therapy, accompanied by a "word of caution" that "other postoperative conditions mimic the withdrawal rebound syndrome and are probably far more common than the syndrome itself." In the only randomized trial of withdrawal in patients undergoing noncardiac surgery, Ponten *et al.* in 1982 reported on 48 patients, all with hypertension and/or ischemic heart disease randomized to either preoperative withdrawal or continuation.[12] They noted "high and unstable heart rate" during both intubation and extubation in the withdrawn group, and decreased blood pressure in all patients during induction of anesthesia, most evident in the continued group. In a subset of patients instrumented with pulmonary artery catheters, continued patients manifested lower cardiac index and stroke work with higher wedge pressure and systemic vascular resistance. ST-segment changes were more common in withdrawn patients, whereas myocardial infarction (MI) was *more common* in the continued group (4 of 11 *vs.* 0 of 9 patients with postoperative enzyme measurements). In their conclusion, the authors recommended continuation of β-blockade, but with the caveat that any benefits are obtained "at the expense of a hypokinetic circulation" suggesting concomitant vasodilator therapy to offset these effects.

Throughout the 1980s, cardiologists debated the existence of a specific β-blocker withdrawal syndrome and whether it occurred with the increasingly popular β1-

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* Available at: http://en.wikipedia.org/wiki/Potter_Stewart. Accessed June 28, 2009.

† The actual wording of this recommendation is "β-blockers should be continued in patients undergoing surgery who are receiving β-blockers to treat angina, symptomatic arrhythmias, hypertension, or other ACC/AHA class 1 guideline indications," and it is accorded a level of evidence of "C" ("very limited [1–2] population risk strata evaluated").

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selective agents. Comparing hemodynamic effects of withdrawal of either nonselective or selective agents in normal volunteers, Ross *et al.* reported rebound increases in heart rate when subjects were withdrawn from therapy of at least 1 week, but not after only 4 days of treatment.[13] Walker *et al.* extended these observations to patients with clinically significant angina withdrawn for 6 days from chronic atenolol therapy.[14] Despite worsening of angina in 3 of 20 patients, no clinically significant events occurred. Mean daily heart rates increased from 61 to 77 beats per minute by day 5. They concluded that the increase in heart rate was only consistent with withdrawal of the expected therapeutic effect. In what remains the most controversial study on this topic, Croft *et al.* analyzed 39 patients withdrawn from propranolol during acute MI.[15] Despite a higher incidence of chest pain during the first 24 h, no differences were noted in biomarker release, estimated infarct size, ejection fraction, or clinical outcomes. The authors conclude that if indicated, β-blockade can be withdrawn during acute infarction and speculate that despite its short half-life, the cardiac effects of propranolol extend to 24–72 h. Other clinical studies demonstrated rebound sensitivity to isoproterenol stimulation testing, with or without changes in resting hemodynamics.[16,17] In a detailed perioperative study, Dagnino and Prys-Roberts specifically recommended such testing for perioperative use.[18] Marty *et al.* were among the the first to demonstrate acute changes in β-receptor sensitivity in response to intraoperative adrenergic activation (increased receptor density with decreased isoproterenol affinity).[19]

The issue was largely dormant until the late 1990s, revived by the controversy that 8 of the 101 placebo patients in the seminal Atenolol trial were acutely withdrawn from unspecified β-blocker therapy.[20] In a subsequent letter to the editor, Mangano noted that the 2-yr cardiac mortality of these patients was identical (12%) to other placebo patients, while Wallace *et al.* noted the absence of any hemodynamic or holter ischemia findings in them.[21,22] The implication appears that perioperative mortality was unaffected. The most widely cited study proscribing withdrawal is the retrospective study of Shammash *et al.*[23] Pharmacy records of 140 patients undergoing vascular surgery at two centers in the mid-1990s were retrospectively examined. Of the eight patients withdrawn from β-blockers, three with strong contraindications to continuation, mortality was 50% *versus* 1.5% in the remainder, resulting in an extraordinarily high odds ratio of 65. Discontinuation of other cardiac medications was also associated with adverse outcomes, but of a significantly smaller magnitude. However, the small number of events and patients must be considered a major concern for regression model overfitting.[24]

Recently, Hoeks *et al.* implied that perioperative discontinuation was associated with long-term mortality (1 yr) in an observational survey of 711 patients undergoing vascular surgery.[25] Preoperative risk variables, including Revised Cardiac Risk Index factors, were assessed.[26] Use was grouped as continuous (40%), no use (53%), discontinued (3%), or no use at time of surgery but with use at discharge (4%). Postoperative contraindications to continued therapy were not reported. A propensity score for the "likelihood of continuous use" using preoperative variables only, was used in a regression model. The authors note that most nonusers were low-risk, whereas half of the treated patients had two or more Revised Cardiac Risk Index factors. In-hospital (24%), 30-day (24%), and 1-yr mortality (38%) were highest in the discontinued group. It is notable that a higher proportion of patients in the discontinued group underwent open vascular (*vs.* endovascular) procedures (86%) compared to the continued group (48%), a factor not clearly considered by the authors that may have independently influenced mortality.

This brings us to the current report of van Klei *et al.*, a retrospective cohort study of 5,158 patients undergoing elective hip or knee arthroplasty at a tertiary hospital modeling associations of β-blocker prescription (ordered on day of surgery and continued, ordered on day of surgery and discontinued, or never ordered on the day of surgery) with perioperative MI (POMI) the primary outcome.[1] Study data were obtained exclusively by linking administrative and clinical databases. A propensity score for the probability of prescription on hospital admission, was used as a covariate in regression models evaluating the association of the three groups, adjusted for clinical covariates, with the outcomes of interest. Preadmission outpatient use was not considered, and no other cardiovascular medications were captured. β-blockers were ordered in 18% of patients on the day of surgery, a group that was older and sicker (see table 1 in van Klei *et al.*[1]). In 25% of these patients, therapy was discontinued at some point, although the reasons for this are not reported. Of the 77 patients in the study sustaining POMI (1.5%), 22 of 740 (2.9%) occurred in the continuous group, 20 of 252 (7.9%) occurred in the discontinued group, and 35 of 4,166 (0.8%) occurred in the no β-blocker on admission group. Logistic regression models, without and after covariate adjustment, yielded odds ratios (OR) of 10 (95% confidence interval [CI] 5.8–18; $P < 0.01$) or 2.0 (1.1–3.9; $P < 0.04$), respectively, for the association of discontinuation of β-blocker with POMI. Associations with mortality (1% of patients) were ambiguous (likely related to the lower event rate), as discontinuation was only marginally associated with death (based on the lower limits of the 95% CI), OR 2.0 (1.0–3.9), whereas continuation was not "protective" with an OR 0.5 (0.2–1.2). Given the absolute requirement for a patient to be either dead or alive, this is problematic, pointing out the need for consistency between correlated variable states in the modeling process. An intriguing observation related to the topical subject of perioperative anemia, somewhat different than that

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postulated to be a prime "culprit" for morbidity in the PeriOperative Ischemic Evaluation Study, was the increased risk of POMI in *discontinued* patients with postoperative hemoglobin less than 100 g/l.[27–29]

Given the nonrandomized design, it is important to appreciate this study's limitations, particularly the "unmeasured confounders."[30] These include use of inpatient pharmacy data alone, precluding categorization of patients into "acute" or "chronic" users (or for what indication), use of troponin elevation alone with no uniform surveillance protocol for POMI, and lack of transfusion data. Other factors include lack of description of the type of pharmacy ordering system and what type of reordering process was involved after surgery. It is unclear whether ordered prescriptions corresponded to medication administration. Use in the operating room or recovery units is not specifically mentioned. No data on anesthetic techniques, pain management strategies, and pain score levels, all covariates influencing a specific patient's degree of adrenergic activation, are presented. Most germane is lack of hemodynamic data. Although physiologic data are not reported in pharmacoepidemiologic studies (*e.g.*, those using prescription data to estimate drug use in large populations), a growing trend from tertiary hospitals or integrated health care systems with clinical information systems, is the mining of "data warehouses" for key physiologic covariates.[31,32]

The use of propensity adjustment is considered an advance in analysis of observational data sets. However, the optimal method for assessing covariate balance remains controversial.[33] Although consideration of this topic is beyond the scope of this discussion, current literature emphasizes patient-matching techniques over covariate adjustment alone (the predominant technique used by van Klei *et al.*).[34] The advantage of matching is that it allows the reader to easily discern balance of critical covariates between exposed and nonexposed groups and the authors to use simpler paired statistical comparisons. The multiple regression models used in the current study are complex. It is possible that alternate approaches might lead to different estimates of treatment effects.

A particular strength of this study is consideration of a homogenous surgical population. Much of the current controversy is based on an attempt to impose one protocol on a wide spectrum of surgical procedures with varying hemodynamic, hormonal, or other unappreciated physiologic stresses and collinearity among patient subgroups and the type of surgery.[35]

If the findings of this study are accurate, then it begs the questions: why would a patient be withdrawn from a life-saving medication, and what is the mechanism for morbidity? A common scenario is failure to order a patient's outpatient medication in the inpatient setting. Given the stereotype of the orthopedic surgeon exclusively fixated on surgical issues, is it possible that the busy surgeon simply forgot to reorder it postoperatively? If so, newer hospitalist-based comanagement care strategies reported for orthopedic surgical services may be effective in reducing perioperative complications.[36] In the absence of hemodynamic data, we can't be assured that discontinued patients developed prolonged tachycardia, an important etiologic factor for perioperative ischemia and POMI.[37]

What if a β-blocker is inadvertently discontinued? Although class effects in treatment of specific medical conditions for three major β-blocker types have been described (*e.g.*, nonselective, β1-selective, intrinsic sympathomimetic activity), there remains controversy about whether this is a valid approach.[38,39] Despite enthusiasm for the use of β1-selective agents, a recent comparison of carvedilol (a nonselective agent with α-blocking effects and antioxidant effects) to metoprolol succinate reported inhibition of both hemodynamic responses to dobutamine stress *in vivo* and isoproterenol-induced increases in force of contraction in excised atrial segments *in vitro* beyond its plasma elimination (not noted with metoprolol), possibly resulting from binding to an allosteric site on the β-receptor.[40] It is well described that different β-blockers have different pharmacokinetics and routes of elimination, some of which may change dynamically in the perioperative period (*e.g.*, renal insufficiency influencing atenolol elimination).[41] Thus, any firm clinical rules grouping different β-blockers together is problematic, given pharmacokinetic, pharmacodynamic, and more recently recognized pharmacogenomic differences.[42–44] Postoperatively, anemic, hypovolemic, or excessively vasodilated patients may present with elevated heart rate and marginal blood pressure. Predicting what will happen day by day and how a particular patient will respond to continuation of β-blockade, particularly when other sympatholytic treatment modalities are used, remains controversial.[45]

Most of our hemodynamic management strategies have blended anesthesia clinical research with the cardiologic wisdom of the day. This rich interface generates tension to alter clinical practice over epochs of time. It is telling that the Clopidogrel and Metoprolol in Myocardial Infarction Trial, a 45,852 patient cohort demonstrating that aggressive early β-blocker use in the acute phase of ST-elevation MI was hazardous, had similar findings of efficacy and adverse safety issues to the PeriOperative Ischemic Evaluation Study study.[29,46] The impact of the Clopidogrel and Metoprolol in Myocardial Infarction Trial is reflected in the new 2008 American College of Cardiology/American Heart Association Performance Measures for ST-Elevation and Non-ST-Elevation MI, in which the sole requirement for β-blockade is now limited to prescription at the time of hospital discharge only (in the absence of contraindications).[47] Although the clinical settings between the two have obvious differ-

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ences, the outcomes of interest have distinct similarities and should give pause for thought.

Do the results of van Klei *et al.* confirm the American College of Cardiology/American Heart Association Guidelines Group Class 1 Level of Evidence C recommendation, and is there really enough evidence to support this designation? I would answer a qualified yes to the latter, but a definite no to the former. This report should remain in the realm of hypothesis generation, given its sole reliance on preoperative risk variables to model postoperative drug discontinuation, lack of ability to discern between patients started acutely or maintained chronically on β-blockers before hospitalization, and lack of consideration of multiple unmeasured confounders. We need abundant data to develop protocols considering the intersection of a particular patient with varying perioperative stressors. However, the vast majority of patients encountered in routine practice should be, and can easily be, continued on β-blocker therapy. A substantial percentage may benefit from a transient increase in dose, given the common and generally adverse clinical scenario of early postoperative adrenergic activation. Forgetting to order (or discontinue based on obvious new contraindications) a chronic or newly instituted medication is never acceptable and should always be considered a breach of quality medical care. Hospitals should actively implement computerized means to prevent this. Yet, we also deal with many patients to whom, less than two decades ago, cardiologists would never have dreamed of prescribing a β-blocker.[48] Many of these practitioners make treatment decisions for ambulatory patients or those hospitalized for limited indications with a stable blood volume. The perioperative environment is rarely that tidy. We must also remain open to use of new but as-of-yet untested medications (*e.g.*, "pure" bradycardic agents lacking myocardial depression such as ivrabadine) and seemingly contradictory treatment paradigms (*e.g.*, combined inotrope and β-blocker therapy) that may ultimately have a more favorable risk-benefit profile than our current strategies.[49,50] Given the historical, clinical, and statistical ambiguities involved in this arena, it is abundantly clear to me that, when it comes to continuing β-blockade postoperatively, *I often don't know it when I see it!* Just like the late Justice Stewart, my opinions may ultimately be shown to be untenable; like that erstwhile gentleman, I will gladly change them as indicated.

Martin J. London, M.D., Department of Anesthesia and Perioperative Care, University of California, San Francisco. londonm@anesthesia.ucsf.edu

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