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Anesthetics, Coronary Artery Disease, and Outcome: Unresolved Controversies

CORONARY ARTERY DISEASE (CAD) continues to be one of the most significant diseases confronted by the anesthesiologist. The incidence of CAD in surgical patients is high; perioperative cardiac morbidity remains excessive; and the annual cost ranges in the billions of dollars. As a result, a substantial amount of anesthesia research is focused on CAD, ultimately in an attempt to identify the most important factors affecting perioperative morbidity. Among the most frequently studied factors is anesthetic choice: is there truly a difference between anesthetics? If so, is any one anesthetic particularly indicated (or contraindicated) in the patient with CAD? Although these questions have been addressed repeatedly over the past 30 years, considerable controversy persists.

It is clear that the perioperative period is particularly stressful. Compared with ambulatory patients with CAD, anesthetized patients with CAD undergoing surgery are subjected to greater hemodynamic and catecholamine changes and have a higher incidence of dysrhythmias and myocardial ischemia. It is unclear whether the anesthetic *per se* prevents or causes these physiologic changes and complications. Anesthetics have been shown to increase coronary vascular reserve, decrease the severity of experimentally induced myocardial ischemia, and even improve the tolerance to pacing-induced ischemia.[1–3] However, anesthetics have also been shown to alter coronary blood flow and autoregulation, produce coronary steal, and cause myocardial ischemia.[4–10] Only with further physiologic study can we resolve such discrepancies.

But are these physiologic issues moot? Does it really matter whether a particular anesthetic causes marked physiologic change, coronary steal, or even myocardial ischemia if outcome remains unaffected? What are the conclusions of the outcome studies addressing anesthetic choice? Over the past 35 years, approximately 27 cardiac outcome studies have been conducted in patients with or at risk for CAD undergoing surgery.* Of these, 11 investigated the question of anesthetic choice, and ten of 11 concluded that anesthetic type did not affect outcome. Only one study, by Rao *et al.*,[11] found a difference between anesthetics: narcotic-nitrous oxide-relaxant anesthesia was associated with a higher incidence of myocardial reinfarction. Most of the evidence therefore suggests that anesthetic choice has little effect on outcome.

Do these outcome data resolve the issue? Unfortunately not. Although these 11 studies included more than 3,000 patients, they were limited in design and methodology. Five of the 11 were retrospective, resulting in incomplete and nonstandardized data collection. Of the six prospective studies, only two thoroughly measured cardiac outcomes and none used a random anesthetic assignment. The outcome studies, although ultimately necessary to resolve the question of anesthetic choice, have not been sufficiently rigorous to justify firm conclusions; and the physiologic studies, although rigorously performed, have yielded conflicting results. Thus, the controversy continues.

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* For purposes of this discussion, only general anesthetics will be considered. A number of studies have addressed the question of regional *versus* general anesthesia in the patient with CAD, and have concluded that only transurethral prostatectomy performed under spinal anesthesia or ophthalmologic procedures performed under local anesthesia may have significant advantage over general anesthetics. A complete listing of the 27 studies can be obtained from the author.

In this issue of ANESTHESIOLOGY, we are presented with two new prospective outcome studies addressing this issue of anesthetic choice in a total of 2,106 patients with CAD (Slogoff and Keats;[12] Tuman *et al.*[13]). Both sets of authors are to be commended for conducting such large-scale prospective studies. The potential impact of these studies is significant, and they therefore merit close scrutiny regarding study design, methods, interpretation of results, and applicability of findings. Before proceeding with these, it is worth commenting on the general model used in both studies.

The "Prebypass-CABG" Model. Both authors have studied the effects of anesthetic choice using a cardiac surgery model. Specifically, they question whether the choice of an anesthetic administered before bypass has a significant impact on prebypass ischemia, perioperative myocardial infarction (MI), or cardiac death. But is this an appropriate model for studying anesthetic choice? The advantages of the model include: 1) the surgery is a single type; 2) the population is relatively homogeneous, allowing comparable demographics in the study groups; 3) the preoperative disease state is well documented; 4) the preoperative cardiac therapy usually is maximal; and 5) the perioperative monitoring, therapy, and care is intense and focused. The disadvantages of the model include: 1) CABG surgery represents <2% of all surgery; therefore, the results may not be applicable to the other 98% of patients undergoing noncardiac surgery; 2) the prebypass period may not be the most critical, as a recent study suggests;[14] consequently, the effects of anesthetics/analgesics administered during other periods (postbypass, ICU) may have greater import; and 3) multiple surgical and other confounders exist, such as the adequacy of myocardial revascularization and cardioplegia, and may have an independent (deleterious or beneficial) effect on outcome. Thus, the "prebypass-CABG" model provides a relatively homogeneous patient population and surgical type, but it is a difficult, complex model with multiple confounders that may not readily allow generalization of the results.

Given the limitations of the model, what conclusions can we draw regarding the studies of Slogoff and Tuman? These studies, although performed at different institutions, appear to have a number of similarities, including: size (Slogoff—1012 patients, Tuman—1094 patients), patient demographics, and incidence of perioperative MI (4.1%, 4.1%) and mortality (1.7%, 3.1%). More importantly, they have come to a similar conclusion: the choice of prebypass anesthetic does not affect cardiac outcome. However, each of these studies has individual strengths and weaknesses that affect the interpretation of their data.

The strengths of the Slogoff and Keats' study include a large study population, randomization of the anesthetic, homogeneity between study groups, and use of an intermediate "outcome" measure—prebypass ischemia—to assess possibly more subtle differences between anesthetics. However, their study also raises a number of questions. First, as in their previous studies,[15,16] perioperative MI, a major outcome variable, was assessed using only one postoperative electrocardiogram (ECG) (POD1) and only one CK-MB determination (10 h postbypass). Additionally, the criteria for diagnosis of an MI required both ECG change (Q, LBBB) *and* CK-MB > 80 U/l. Consequently, only early (<18 h) and large transmural infarcts would be detected, as indicated by the very low infarction rate of 4.1%, one of the lowest reported in the literature. If anesthetics have only "moderate" effects on outcome, such as extending an area of necrosis or producing a subendocardial MI, then using insensitive determinants of MI, as in their study, would obscure the relationship between anesthetics and outcome. Second, the incidence of myocardial ischemia in their current and prior studies is substantially higher than that reported by other investigators.[14,17] In fact, despite using *intermittent* ECG monitoring, their incidence of ischemia is higher than that found in other studies which used *continuous* ECG monitoring with two or even more (12) leads. What are the possible reasons for these potentially important discrepancies?

A number of factors may play a role, including the patient population, the detection system, and the criteria used for diagnosis of ischemia. Differences in the patient population or patient management between their institution (Texas Heart Institute) and others may be factors. For example, approximately 50% of the patients studied by Slogoff and Keats were receiving chronic β-blocker therapy, yet β-blocker therapy was discontinued preoperatively in more than half of these patients. Since β-blocker withdrawal has been shown to precipitate perioperative ischemia,[18] Slogoff and Keats' unusually high incidence of ischemia on arrival (29.3%) is therefore not surprising, especially in light of its relationship to elevated arrival heart rates. Thus, their patients may be different from those of other studies in which β-blockers are continued until surgery. Furthermore, since they found that the best predictors of prebypass ischemia included ischemia on arrival and failure to receive preoperative β-blockers, their prebypass ischemia may have been somewhat "pre-ordained." If so, then the high incidence of prebypass ischemia may mask the ability of this study to identify the independent effect of other factors, such as the choice of anesthetic.

Differences in the detection systems may also be responsible for differing rates of ischemia detection. ST detection sensitivity is affected by lead location (lateral *vs.* inferior) and lead type (bipolar *vs.* unipolar), as well as the frequency response of the ECG system.[19] The recommendation of the American Heart Association is 0.05 to 100 Hz filtering.[20] Narrow band width filters (4–30

Hz), such as those used for clinical rhythm monitoring, may distort the ST segment and decrease R-wave amplitude. False positive ST depression or elevation may result. Finally, although ST criteria are generally "standardized" (1 mm depression at J + 80 msec), their interpretation can be quite subjective. Deviations in the ST segment are particularly difficult to interpret when the changes are small (<1.5 mm), the baseline is abnormal (as in >25% of patients with CAD), T-wave changes occur, R-wave amplitude varies, or heart rate increases. These potential differences in ST interpretation can have a substantial effect on the reported incidence, character, and import of perioperative myocardial ischemia.

To summarize, the strength of Slogoff and Keats' work is that it is a large, prospective, randomized study, but it has a number of limitations that restrict application and generalization of its findings.

The study of Tuman *et al.* also has a number of strengths, including the large number of patients studied (1094), the homogeneity between study groups, and the use of multiple measures to assess cardiac outcome. Among the limiting factors, the most important is the lack of randomization. The five primary anesthetics were not randomly assigned, but were chosen by the attending anesthesiologist based on individual preference. Certain primary anesthetics, such as moderate-dose fentanyl, were selected more frequently (345 patients); and others, such as halothane (the only primary inhalational anesthetic), were selected much less frequently (47 patients). In addition, the use of pulmonary artery (PA) monitoring was not standardized; its use ranged between 25.5% and 60% across the anesthetic groups. Since the treatment protocol was, in part, based on data derived from the PA catheter (wedge pressure, vascular resistance), the treatment criteria may not be uniform across these groups, and outcome may have been affected. Although patient characteristics did not differ between the anesthetic groups (Tuman *et al.*, table 1), the non-randomized selection process makes comparison of these anesthetic groups that much more difficult.

A second limitation of the Tuman study is the choice of primary and secondary anesthetic subgroupings. The five primary anesthetics chosen included a rarely used anesthetic, diazepam-ketamine, and excluded a controversial and commonly used anesthetic, isoflurane. Furthermore, in 60% of patients, the primary anesthetic was supplemented with a secondary inhalational anesthetic (halothane, enflurane, isoflurane), resulting in a total of 17 different anesthetic combinations. It is therefore not surprising that no difference in outcome was found between either the primary or secondary anesthetic groups.

The third limitation is their outcome measurement methods. Two outcomes, postoperative ECG ischemia and serious dysrhythmias, were measured intermittently and only every 4 h. Thus, many of these outcomes may not have been detected. The criteria for assessment of MI, new Q-waves, *and* CK > 80 U/l allow detection of only large transmural MIs. As previously discussed, this may be too stringent a criterion and may obscure the relationship between anesthetics and more subtle outcomes, such as subendocardial MI.

What can we conclude? These studies are noteworthy, for they are large, prospective outcome studies examining the important and controversial question of anesthetic choice. The results of both studies support the hypothesis that anesthetic choice has little bearing on outcome in the patient with CAD. In fact, they also appear to support the position that isoflurane, when used as a primary or secondary anesthetic, is *not* deleterious in the patient with CAD (if hemodynamics are controlled). However, both studies have limitations. Their model addresses only patients undergoing CABG surgery, and their results cannot be generalized to the large class of patients with CAD undergoing noncardiac surgery. Questions regarding ischemia incidence (Slogoff), anesthetic randomization (Tuman), and outcome measurement (both) are germane and affect the interpretation of their results. More importantly, such questions preclude resolution of the issue of anesthetic choice (particularly regarding isoflurane), even in patients undergoing CABG surgery. Perhaps both studies should be viewed as forerunners of a series of randomized, prospective outcome studies addressing this issue. This perspective enables us to profit from both their strengths and weaknesses as we pursue the question of anesthetic choice. Only rigorous outcome studies will allow us to resolve the controversies regarding the effects of anesthetics on coronary blood flow, myocardial ischemia, and cardiac outcome.

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