Is Anesthesia Beneficial for the Ischemic Heart? III.

Two previous editorials bearing the above title have suggested that anesthetics, per se, do not specifically influence the heart at risk for myocardial ischemia. Rather, it has been proposed that the effect of anesthetics on myocardial oxygen balance is mediated solely by factors influencing myocardial oxygen supply and demand. In the subsequent years, a number of reports have appeared to confirm this opinion.

These studies did not address whether, and in what circumstances, an anesthetic that interferes with coronary autoregulation might be hazardous. Normally, coronary blood flow is related to myocardial oxygen demand so closely that coronary arteriovenous oxygen content difference remains stable. When autoregulation is impaired by a potent coronary vasodilator, coronary blood flow is elevated inappropriately relative to oxygen demand. Therefore, oxygen extraction per unit volume of blood decreases, myocardial arteriovenous oxygen content difference decreases, and coronary venous oxygen saturation increases. No harm is done when coronary arteries are normal. Ironically, this property may cause harm when coronary artery stenoses are present.

It is clear that coronary vasoconstriction, or a decrease in inflow pressure (i.e., hypotension), in the presence of stenosis may produce ischemia. It is more difficult to understand why coronary vasodilation should do so. However, Reiz et al. demonstrated electrocardiographic and metabolic evidence of myocardial oxygen imbalance and elevated coronary venous oxygenation during isoflurane anesthesia associated with a low systemic arterial pressure and coronary vasodilation. In three patients, the imbalance persisted despite pharmacologically returning the blood pressure to control levels while maintaining the heart rate constant. (Though this also partially reversed the decline in calculated coronary vascular resistance, myocardial oxygen extraction remained low, providing evidence of persistent coronary vasodilation.) This study suggests that redistribution of coronary blood flow, often termed "coronary steal," may be a real phenomenon during isoflurane anesthesia.

There now is convincing evidence in laboratory animals that isoflurane is indeed a coronary vasodilator. However, extensive investigations into the nature of "coronary steal" have indicated that factors in addition to coronary vasodilation are necessary to produce such maldistribution of coronary blood flow. Fam and McGregor noted that the site of coronary vasodilation was important. Dipyridamole, which dilates small intramural arterioles, produces the condition, while nitroglycerin, which dilates large epicardial conducting arteries, does not. At the present time, the site of isoflurane's coronary vasodilating property is not known.

Others have proposed that established collateral vessels, tachycardia, and proximal stenosis of the conducting vessels supplying collaterals are required to produce redistribution of myocardial perfusion from ischemic to nonischemic areas. Becker suggested that "steal" is an inappropriate name because the increased ischemia is the result of decreased collateral perfusion pressure. Another variant of "steal," which produces redistribution of coronary blood flow from endocardium to epicardium, has been described. It has been observed with adenosine injection distal to a fixed intraluminal coronary artery stenosis and in exercising dogs with a coronary stenosis. When coronary vasodilation was produced by nifedipine, a drug that also possesses negative inotropic effects, redistribution was lessened and evidence of ischemia was not observed. Isoflurane is also a vasodilator with negative inotropic effects.

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In this issue of Anesthesiology, Tarnow et al. report that isoflurane–nitrous oxide anesthesia protects against pacing-induced ischemia in patients with documented ischemic heart disease. What is the reason for the marked disparity between the Tarnow and Reiz publications? This question cannot be answered with certainty, but a number of differences may play a role. First, Tarnow’s patients were sedated before invasive monitoring, and basal cardiovascular dynamics were lower than those of Reiz’s patients. The importance of this is unclear, but the rate of change of hemodynamic variables may play a role. Second, a marked difference existed in the patient population. Thirteen of Reiz’s 21 patients were being treated with digoxin, a diuretic, or both, suggesting a significant incidence of congestive heart failure, while patients with congestive failure were specifically excluded from Tarnow’s series. Third, Reiz’s patients were older (mean age 68.3 yr, range 55–80 yr) than Tarnow’s patients (mean age 54.8 yr, range 41–65 yr).

In summary, Tarnow’s patients were younger, less seriously ill, and more typical of the average ischemic heart disease patients previously studied.4-6 We conclude that, certainly, interference with coronary autoregulation may adversely affect distribution of coronary blood flow despite normal-appearing systemic hemodynamics. However, the circumstances under which isoflurane may produce such redistribution are unclear.

The publication in this issue of Anesthesiology by Kleinman et al.19 is also disturbing with respect to anesthetic management of patients with ischemic heart disease. Kleinman’s group estimated myocardial perfusion by thallium-201 (TI-201) scintigraphy before surgery, immediately following tracheal intubation, and a week later in a group of patients with ischemic heart disease and well-preserved left ventricular function. A high and equal incidence of new perfusion defects followed tracheal intubation unrelated to changes in any hemodynamic variable, whether the anesthetic was fentanyl- or halothane-based. Surprisingly, patients without perfusion defects increased their heart rate more than those patients with defects. Neither ischemic electrocardiographic changes in lead V5 nor alterations in pulmonary capillary wedge pressure occurred in any patient.

This study raises two questions. First, is a TI-201 perfusion defect synonymous with myocardial ischemia? As Kleinman et al.19 have noted, a TI-201 scan only measures relative perfusion of a given area in the heart. Decreased activity indicates a regional disparity of perfusion, but not necessarily ischemia. As noted previously, decreased blood flow even to a region distal to a stenosis is not accompanied by evidence of oxygen imbalance if there is a sufficient decrease of myocardial oxygen demand at the same time.15 The fact that a major determinant of myocardial oxygen demand, heart rate, was lower in the patients with TI-201 defects may indicate that the decreased perfusion was not associated with oxygen deficit. Although the only patient with a perioperative myocardial infarction had a new perfusion defect after intubation, the persistent postoperative defect (indicating infarction) was in a different region, so the relevance of the initial TI-201 defect still appears questionable.

A point of perhaps greater importance is the definition of a so-called gold standard for detection of myocardial ischemia. Currently, the metabolic consequences (efflux of lactate, potassium, hydrogen ion, and adenosine triphosphate breakdown product) of tissue hypoxia and regional wall motion abnormalities appear to be the best available indices. Although the former can now be detected noninvasively in humans (positron emission tomography),22 the procedure is not feasible clinically. There is more hope for the detection of wall-motion abnormalities in the operating room. The precordial cardiokymograph and the transesophageal echocardiogram both show promise of detecting wall-motion abnormalities relatively noninvasively and on-line in the clinical setting. However, wall-motion abnormalities are not completely specific for ischemia, and no studies yet performed indicate that detection and, more importantly, treatment of such abnormalities affect the perioperative well-being of patients. Although Keats and Slogoff documented that ischemic electrocardiographic changes prior to the initiation of cardiopulmonary bypass in patients undergoing coronary artery bypass grafting are related to the incidence of perioperative infarction,25 metabolic or wall motion changes are more sensitive indices of ischemia. Thus, the implications of the data reported by Kleinman et al. may require further refinement.

Assuming that the TI-201 defect observed by Kleinman et al. indicates ischemia, the second question is the etiology of this ischemia. Neither fentanyl nor halothane is a potent coronary vasodilator, so redistribution of perfusion on that basis seems unlikely. Coronary vasospasm recently has become widely recognized as a cause of ischemia when there is no accompanying evidence for decreased oxygen supply or increased demand.2627 Although it previously was considered rare, coronary vasospasm superimposed on anatomic coronary stenosis is now a frequent occurrence. Although most commonly caused by sympathetic nervous system stimulation, other factors, including hypersensitivity of the pathologic coronary artery, may be involved as well.28 Review of hemodynamic data from previously published studies of ischemic episodes during anesthesia suggests that coronary vasospasm may be more important than previously recognized.29-31

If the incidence of myocardial ischemia without detectable changes in myocardial oxygen supply–demand balance or the electrocardiogram approaches the 45% incidence of TI-201 perfusion defects after tracheal intu-
bation\textsuperscript{19} or the 25\% incidence of cardiokymographic changes in patients with LAD disease,\textsuperscript{23} and if such ischemia is associated with perioperative morbidity, then the conclusions of the previous two editorials are incorrect. It may not be sufficient to “keep the determinants of myocardial oxygen consumption as close to the unanesthetized angina-free value as possible while maintaining coronary perfusion pressure.” Rather, such conditions may represent a necessary base from which better clinical methods for detecting and effectively treating myocardial ischemia must be discovered and used for optimal patient care.

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References


A Valid Demonstration of Barbiturate-induced Brain Protection in Man—At Last

TO MY KNOWLEDGE, there are only three definitive valid studies in man that have examined for possible brain protection induced by barbiturate therapy in three very different clinical circumstances. Abramson et al.\(^1\) reported in an abstract that a randomized clinical trial of thiopental therapy following cardiac arrest failed to demonstrate even a suggestion of improved outcome. Ward et al.\(^2\) reported that randomized pentobarbital therapy in acute head-injury patients also failed to yield even a suggestion of improved outcome. While, in this issue, Nussmier et al.\(^3\) demonstrate that randomized thiopental therapy during certain cardiopulmonary bypass procedures does improve neuropsychiatric outcome. The seemingly divergent results in these three studies should not come as a surprise but, instead, are consistent with the bulk of the evidence derived from multiple animal studies.

Despite some early controversy, animal studies in recent years have failed consistently to yield any data even suggestive of a meaningful beneficial effect for barbiturate therapy, whether given before or after a period of complete cerebral ischemia (i.e., cardiac arrest models).\(^4\)-\(^7\) Indeed, even the initial two positive studies\(^8\)-\(^9\) subsequently were refuted by repeat negative studies.\(^4\),\(^7\) The results from the randomized human trial of thiopental therapy following cardiac arrest\(^1\) should have been largely predictable, and the justification for having pursued that study was questioned by some from the beginning. Why does barbiturate therapy fail to improve outcome in cardiac arrest? One reasonable guess relates to the fact that cerebral metabolic suppression by barbiturates is only possible in a circumstance wherein the EEG remains active. With cardiac arrest, the EEG become isoelectric within 20–30 s and will remain so after resuscitation for many minutes. Thus, if metabolic suppression is the basis for barbiturate-induced brain protection, none should be possible in the event of cardiac arrest.

In head trauma, it is now well established that barbiturates offer an alternative means of decreasing and controlling intracranial pressure (ICP). However, this need not equate to improved outcome. An initial report based on a nonrandomized clinical trial suggested improved outcome,\(^10\) but this was questioned by Miller in a retrospective analysis of outcome in his head trauma patients.\(^11\) The study by Ward et al.\(^2\) confirmed Miller's analysis and conclusions. In the case of head trauma, there were no animal studies that would have permitted any reasonable prediction regarding efficacy of barbiturate therapy (other than the ICP effects).

By contrast, a number of animal studies concerned with various forms of incomplete ischemia have yielded consistent results of improved outcome with barbiturate therapy.\(^12\)-\(^14\) As a result, it is recommended commonly that barbiturates be administered intraoperatively to patients who are about to experience a potential incomplete ischemic insult. Examples of such a possible application include carotid endarterectomy, aneurysm surgery requiring temporary occlusion of the parent vessel, cerebral bypass procedures, and profound levels of induced hypotension. In none of these procedures was there any real hope for a valid randomized study to emerge in order to determine if such treatment is efficacious. In all of these procedures, the expected incidence of new neurologic deficits is relatively low, while the possible causes of any new neurologic deficit are multiple and need not relate to the period of anticipated incomplete ischemia. Under these circumstances, a valid study would be next to impossible.

Slogoff and his associates recognized this void and saw in their population of patients undergoing cardiopulmonary bypass a made-to-order model for examining the

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