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Is Isoflurane Dangerous for the Patient with Coronary Artery Disease?

SINCE ITS INTRODUCTION into clinical practice about 6 years ago, isoflurane has become the most widely used inhalation anesthetic. Its popularity is based on several important attributes.¹ Relative to other inhalation anesthetics, it resists biodegradation, thereby avoiding halogen-induced hepatic and renal toxicity; has low blood solubility, facilitating control of anesthetic depth and promoting rapid recovery from anesthesia; potentiates the effects of muscle relaxants; provides less sensitization to catecholamine-induced cardiac arrhythmias; and causes less depression of myocardial function. In addition, isoflurane is a systemic and coronary vasodilator, reducing left ventricular afterload and work, lowering myocardial oxygen requirements, and reducing coronary vascular resistance. Perhaps paradoxically, it is this latter effect on the coronary circulation which may make it dangerous for the patient with coronary artery disease.

Isoflurane is clearly a myocardial depressant, albeit less so than halothane or enflurane. Isoflurane has been shown to depress contractility of isolated cat papillary muscles² and to produce dose-dependent decreases in left ventricular performance and oxygen consumption *in vivo*.¹ Despite a few contrary reports,^{3,4} the bulk of evidence also indicates that isoflurane is a potent systemic and coronary vasodilator. Gelman *et al.* found that, in dogs, isoflurane decreased vascular resistance in the heart and brain while increasing resistance in the preportal region.⁵ In patients, blood pressure has been shown to fall concomitant with

a decrease in systemic vascular resistance⁶⁻⁸ and a rise in skin and muscle blood flow.⁶ Although Merin³ did not find a decrease in coronary resistance in the dog as isoflurane concentration was increased from 1.7 to 3.3%, control measurements were not made, and coronary vasodilation occurring between 0 and 1.7% could have been missed. Interestingly, studies by Lundeen *et al.*⁴ and Manohar and Parks⁹ in swine have both failed to show coronary vasodilation with isoflurane, suggesting a possible species difference.

The study by Priebe in this issue adds further support to the notion that, in clinically useful concentrations, isoflurane represents a potent coronary and systemic vasodilator.¹⁰ In higher concentrations, no further coronary dilation occurs, but myocardial depression becomes predominant, leading to a further decrease in arterial pressure and cardiac output, and a fall in coronary blood flow related to the reduction in perfusion pressure. Priebe adds the interesting information that isoflurane has no significant effect on the pulmonary circulation.

If isoflurane is a coronary vasodilator, where is its site of action? From the results cited in the previous paragraph, it is clear that isoflurane must dilate at least the arterioles, which constitute the major site of coronary vascular resistance. Most studies have shown an increase or no change in myocardial blood flow in the face of a reduction in arterial pressure and a decrease in myocardial oxygen consumption, consistent with a direct dilating effect on coronary resistance vessels ("luxury perfusion").^{8,11} The study by Sill *et al.* in this issue provides the first direct evidence that the dilating effect of isoflurane is limited to the small coronary vessels.¹² Using quantitative coronary angiography, the authors found no change in the caliber of the epicardial coronary arteries with 0.75-2.25% end-tidal isoflurane, despite a doubling of myo-

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cardial blood flow. Isoflurane thus belongs to the class of vasodilators having predominantly small vessel effects with little or no action on epicardial conductance vessels. Other compounds in this class include adenosine, dipyridamole, papaverine, and carbochromen.^{13,14} In contrast, effective anti-ischemic agents, such as nitrates and calcium channel blockers, have predominant effects on large epicardial arteries.¹⁵

Given the fact that isoflurane is a small vessel-type coronary vasodilator, it should come as no surprise that isoflurane is capable of producing myocardial ischemia. Although seemingly paradoxical, it is well known that this type of coronary vasodilator can cause myocardial ischemia by diverting flow away from areas of borderline perfusion and limited coronary reserve toward areas that are already adequately perfused. This phenomenon has been termed "coronary steal," and has been convincingly demonstrated to occur in a variety of animal models.¹⁶ Despite the difficulties in accurately measuring regional myocardial flow and ischemia in the clinical setting, there is also considerable evidence to support the existence of coronary steal in humans. Perhaps the clearest demonstration comes from patients being evaluated for coronary artery disease by intravenous dipyridamole infusion combined with thallium imaging. As many as 50% of these subjects have been reported to develop angina and/or electrocardiographic evidence of myocardial ischemia, despite minimal changes in rate-pressure product. This suggests that, despite an increase in total coronary blood flow, flow decreases below baseline levels in one or more regions of myocardium.¹⁷⁻¹⁹ In the absence of a significant decline in arterial pressure or increase in myocardial oxygen demands, ischemia must be attributed to a drug-induced redistribution of flow, resulting in a decrease in flow to borderline perfused regions.

Coronary steal is generally visualized as a reduction in flow to a collateral-dependent region of myocardium, accompanied by an increase in flow to regions perfused antegrade through patent vessels. During drug-induced arteriolar dilatation, resistance falls in both normal and collateral-dependent regions, but the reserve of the latter is exhausted first, leading to a redistribution of antegrade flow in favor of the lower-resistance normal vascular region. Flow decreases in the collateral-dependent region because of a fall in the intracoronary pressure at the origin of the collateral vessels, resulting in a decrease in driving pressure for collateral flow. Ordinarily, only a small pressure gradient exists between the aorta and the small coronary arteries, giving rise to the collaterals, with little change after vasodilator administration. In the presence of epicardial coronary stenoses, however, the pressure gradient is increased at rest, and increases further during downstream vasodilation, apparently because of increased turbulence and energy losses. Coronary steal should,

therefore, be more likely to occur if the coronary arteries providing perfusion for the collateral-dependent region are partially obstructed, and this appears to be the case in animal models.²⁰ On the other side of the coin, "steal" would tend to be moderated by dilatation of the proximal coronary arteries or of the collaterals themselves, since these effects would tend to increase the effective perfusion pressure of the collateral-dependent region. In addition, the presence of large collaterals with low resistance would make "steal" less likely, since greater dilatatory capacity of the collateral-dependent region would be preserved, thereby permitting compensation for the fall in perfusion pressure.

The paper by Buffington *et al.* in this issue clearly shows that isoflurane has the capacity to cause coronary steal in an animal model.²¹ The study utilized dogs with chronically developed collaterals and a completely occluded anterior descending coronary artery. Despite a highly artificial protocol in which total coronary flow was held constant at a moderately reduced level, the results clearly showed that isoflurane was able to create a flow maldistribution with a decrease in the collateral-dependent region and an increase in the normally perfused region, concomitant with a deterioration in collateral zone function.

Another form of "coronary steal" may also occur transmurally downstream from a coronary stenosis. Following vasodilator administration, flow may increase to the subepicardium, but decrease to underlying subendocardium. This flow maldistribution is related to a decrease in coronary pressure distal to the stenosis, combined with the greater dependence of subendocardial flow on perfusion pressure and the earlier exhaustion of subendocardial vascular reserve. The article by Priebe and Foëx in this issue shows that isoflurane-induced hypotension may result in a deterioration of function distal to a coronary stenosis.²²

Getting back to the original question, "Is isoflurane dangerous for the patient with coronary artery disease," the answer is almost certainly yes, in *some* patients, under *some* conditions. Based on its small vessel dilating properties, isoflurane clearly has the potential for causing regional myocardial ischemia in the patient with coronary disease. It has been shown to produce "coronary steal" in an animal model. Even more importantly, Reiz *et al.*⁹ have found electrocardiographic and metabolic evidence of myocardial ischemia produced by 1% end-tidal isoflurane in 10 of 21 patients with stable coronary artery disease. In 2 of 5 patients with signs of ischemia, restoration of aortic pressure resulted in resolution of ischemia, but, in three patients, ischemia persisted. The results suggest that isoflurane-induced ischemia may occur in as many as 50% of patients with coronary disease, and that decreased arterial pressure and redistribution of myocardial blood

flow (coronary steal) may both contribute to the problem. From the previous discussion, patients at highest risk for isoflurane-induced ischemia are those with multivessel disease, although even those with significant single vessel stenoses are candidates for developing subendocardial ischemia. Those patients with multivessel disease and left ventricular failure may be at particularly high risk because of the propensity for high left ventricular filling pressures to exacerbate subendocardial ischemia, as well as because of the danger of myocardial depression related to direct effects of the anesthetic. Unless either the previously mentioned advantages of isoflurane or the adverse side effects of other anesthetics on other organ systems outweigh the potential risk of isoflurane-associated myocardial ischemia, the safest course would therefore appear to be to avoid isoflurane in patients with known coronary artery disease. In addition, if isoflurane is chosen for the patient without demonstrated coronary disease, but with significant coronary risk factors (*e.g.*, older age group, evidence of peripheral vascular disease, known hyperlipidemia), it would seem prudent to monitor the patient carefully for electrocardiographic or hemodynamic signs of ischemia, and be prepared to switch to a different anesthetic agent if any signs of ischemia appear. Clearly, these recommendations await further support from carefully controlled randomized studies in humans in whom different anesthetics are compared with respect to the incidence of, and severity of, ischemic cardiac events.

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