Anesthetic Preconditioning

An Anesthesiologist’s Tale

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ABSTRACT:

**Background:** The hypotheses that isoflurane directly precondition myocardium against infarction via activation of adenosine triphosphate–regulated potassium channels and that the protection afforded by isoflurane is associated with a short-term memory phase similar to that of ischemic preconditioning were tested.

**Methods:** Barbiturate-anesthetized dogs (n = 71) underwent measurement of systemic hemodynamics. Myocardial infarct size was assessed by triphenyltetrazolium chloride staining. All dogs were subjected to a single prolonged (60-min) left anterior descending (LAD) coronary artery occlusion, followed by 3 h of reperfusion. Ischemic preconditioning was produced by four 5-min LAD coronary artery occlusions interspersed with 5-min periods of reperfusion before the prolonged LAD coronary artery occlusion and reperfusion. The actions of isoflurane to decrease infarct size were examined in dogs receiving one minimum alveolar concentration of isoflurane that was discontinued 5 min before prolonged LAD coronary artery occlusion. The interaction between isoflurane and ischemic preconditioning on infarct size was evaluated in dogs receiving isoflurane before and during preconditioning LAD coronary artery occlusions and reperusions. To test whether the cardioprotection produced by isoflurane can mimic the short-term memory of ischemic preconditioning, isoflurane was discontinued 30 min before prolonged LAD coronary artery occlusion and reperfusion. The mechanism of isoflurane-induced cardioprotection was evaluated in two final groups of dogs pretreated with glyburide in the presence or absence of isoflurane.

**Results:** Myocardial infarct size was 25.3 ± 2.9% (mean ± SEM) of the area at risk during control conditions. Isoflurane and ischemic preconditioning produced significant (P < 0.05) and equivalent reductions in infarct size (ischemic preconditioning alone, 9.6 ± 2.0%; isoflurane alone, 11.8 ± 2.7%; isoflurane and ischemic preconditioning, 5.1 ± 1.9%). Isoflurane-induced reduction of infarct size also persisted 30 min after discontinuation of the anesthetic (13.9 ± 1.5%), independent of hemodynamic effects during LAD coronary artery occlusion. Glyburide alone had no effect on infarct size (28.3 ± 3.9%), but it abolished the protective effects of isoflurane (27.1 ± 4.6%).

**Conclusions:** Isoflurane directly precondition myocardium against infarction via activation of adenosine triphosphate–regulated potassium channels in the absence of hemodynamic effects and exhibits short-term memory of preconditioning in vivo.

MORE than two decades ago, isoflurane was rarely used in patients with coronary artery disease undergoing cardiac surgery, in part because of concerns that this volatile agent caused coronary artery steal and might induce episodes of myocardial ischemia.¹ As an anesthesiology resident at the University of Iowa, Iowa City, contemplating a career in academic medicine, I was intrigued by such questions. I also had a strong interest in studying the physiology of the coronary circulation and the effects of anesthetics on its regulation. My first research experience was as a senior resident examining the effects of hyperglycemia and diabetes mellitus in modulating coronary microcirculatory responses to ischemia under the direction of Kevin Dellsperger, M.D., Ph.D. (Assistant Professor, Department of Medicine, and the Cardiovascular Research Center, College of Medicine, University of Iowa). At approximately the same time, experiments conducted in chronically instrumented dogs at the Medical College of Wisconsin, Milwaukee, by David C. Warltier, M.D., Ph.D. (Professor and Vice Chair for Research, De-
partment of Anesthesiology, and Professor of Medicine, Division of Cardiology and Pharmacology and Toxicology), debunked the theory that volatile anesthetic agents caused coronary steal and demonstrated that, although volatile anesthetics were coronary artery vasodilators, their actions were relatively mild when compared with potent vasodilator drugs, such as adenosine.2,3 Thus, contrary to the contention that isoflurane might be dangerous in the setting of coronary artery disease, Warltier et al.4 demonstrated that volatile anesthetics, including isoflurane, enflurane, and halothane, actually protected the heart against ischemic injury and enhanced recovery of stunned myocardium. It was in this productive research environment that I found myself (fig. 1), as a fellow on the Medical College of Wisconsin Anesthesiology Training Grant, a clinical instructor, and Dave Warltier became my mentor. One of our first discussions centered on the relatively unanticipated finding obtained during his earlier work that the actions of volatile anesthetic agents to protect against myocardial injury did not appear to depend on anesthetic-induced decreases in major determinants of myocardial oxygen consumption. Thus, we hypothesized that volatile anesthetics, such as isoflurane, might have direct effects to mediate cardioprotection.

At approximately this time, two other groups were examining the mechanisms responsible for coronary artery vasodilation produced by halothane and isoflurane. Larach and Schuler5 found that halothane-induced coronary vasodilation was blocked by glyburide in an isolated arrested rat heart model, and Cason et al.6 showed that isoflurane-induced increases in regional coronary blood flow were abolished by this same sulfonylurea drug in open-chest swine. Interestingly, sulfonylureas, such as glyburide, are antagonists of adenosine triphosphate–regulated potassium (KATP) channels. These channels are present in the β cells of the pancreas, the brain, vascular smooth muscle cells, and the myocardium. We hypothesized that anesthetic activation of KATP channels might decrease ischemic myocardial injury by reducing intracellular calcium concentrations, a contention supported by the earlier findings of our colleague, Garrett Gross, Ph.D., a professor in the Department of Pharmacology and Toxicology, Medical College of Wisconsin. To my knowledge, Gross was the first to identify the critical role of KATP channels in mediating the beneficial effects of ischemic preconditioning to reduce the extent of myocardial injury.
The experiments we designed to evaluate this hypothesis were conducted in a model of stunned myocardium and were central to the work proposed in a Foundation for Anesthesia Education and Research Young Investigator/Society of Cardiovascular Anesthesiologists Investigator Award. Barbiturate-anesthetized dogs were subjected to repetitive brief periods of coronary artery occlusion and reperfusion to produce myocardial stunning, in the presence or absence of isoflurane, with and without pretreatment with glyburide (fig. 2). Dogs receiving isoflurane demonstrated full recovery of regional contractile function by 60 min after the onset of final reperfusion; however, animals pretreated with glyburide exhibited sustained severe myocardial contractile dysfunction. To my knowledge, these were the first findings to demonstrate isoflurane activation of $K_{\text{ATP}}$ channels as a mechanism responsible for cardioprotection. However, a limitation of the experimental design was that isoflurane was administered before and during the period of myocardial ischemia elicited by repetitive coronary artery occlusion and reperfusion. Therefore, we could not completely exclude an antiischemic effect of isoflurane to decrease myocardial oxygen consumption during myocardial ischemia.

A key question that was left unanswered by our initial investigations was as follows: “Do volatile anesthetics directly precondition the heart?” In 1986, a group of investigators, Murry et al., showed that a brief “preconditioning” period of myocardial ischemia before prolonged coronary artery occlusion decreased the extent of subsequent infarction by nearly 80%. A unique feature of this phenomenon was that the myocardium remained protected for a period after withdrawal of the preconditioning stimulus, this interval was termed the memory of preconditioning. We wondered whether isoflurane could similarly precondition the heart, as observed during ischemic preconditioning and as defined by the presence of a short-term memory phase. Thus, we designed the experiment highlighted in this “Classic Papers Revisited.” Barbiturate-anesthetized dogs were treated with one minimum alveolar concentration of isoflurane for 30 min, and this volatile agent was discontinued 30 min before prolonged coronary artery occlusion and reperfusion. Discontinuation of the volatile anesthetic in advance of left anterior descending coronary artery occlusion allowed us to...
examine whether isoflurane produced a memory effect. The end-tidal isoflurane concentration was undetectable, and hemodynamic values had returned to baseline before the onset of prolonged ischemia. Yet, isoflurane produced a marked reduction in myocardial infarct size (fig. 3). This observation was exciting, and the finding that the beneficial actions of isoflurane were blocked by glyburide confirmed a critical role of K$_{ATP}$ channels in cardioprotection. These results were reported for the first time at an oral session of the Association of University Anesthesiologists annual meeting in April 1997 where the findings were met with considerable enthusiasm. At last, some evidence existed to indicate that an anesthetic could provide a benefit, beyond insensibility and lack of awareness, to patients with coronary artery disease undergoing anesthesia and surgery. Previous exposure to a volatile anesthetic could provide lasting myocardial protection! Although halothane anesthesia had been shown to decrease myocardial necrosis in 1983,$^{10}$ the field of anesthetic preconditioning was primed to take off.

After our initial discovery, multiple groups,$^{11–13}$ including our own (fig. 4), began to examine the mechanisms involved in anesthetic cardioprotection using animal models; and the first human studies were conducted in patients undergoing cardiac surgery. Such investigations confirmed that volatile anesthetics protected the heart against ischemia and reperfusion injury when administered not only before, but after, a period of myocardial ischemia (postconditioning). Interestingly, our findings that volatile anesthetics preconditioned the heart have also been extended to other organs, such as the brain$^{14}$ and liver.$^{15}$ Inhaled anesthetics activated a variety of signaling mechanisms that included membrane-bound receptors, intracellular kinases, ion channels, and NO; they also protected mitochondria. Impressive experimental evidence supported the cardioprotective effects of these agents. However, lingering questions remained regarding the efficacy of volatile

Fig. 3. Isoflurane preconditions myocardium against infarction through activation of adenosine triphosphate–regulated (K$_{ATP}$) potassium channels. The myocardial infarct size expressed as a percentage of the area at risk is shown for each experiment. CON = control; GLB = pretreatment with glyburide; I = administration of isoflurane until 5 min before prolonged left anterior descending (LAD) coronary artery occlusion; I + M = discontinuation of isoflurane 30 min (memory period) before prolonged LAD coronary artery occlusion; I + M + GLB = pretreatment with glyburide followed by discontinuation of isoflurane 30 min before prolonged LAD coronary artery occlusion; I + PC = administration of isoflurane before and during ischemic preconditioning; PC = ischemic preconditioning. * Significantly ($P < 0.05$) different from CON; † significantly ($P < 0.05$) different from GLB; § I + M + GLB significantly ($P < 0.05$) different from I + M. (Reproduced from ANESTHESIOLOGY 1998; 85:794–807, with permission.)

anesthetics in improving long-term outcome in patients with cardiovascular disease.

At approximately this time, the focus of our investigations returned full circle to questions asked during residency and to the study of diabetes and hyperglycemia. We hypothesized that acute hyperglycemia or chronic diabetes might have deleterious effects on cardioprotective signaling mechanisms and that impaired “preconditioning” might explain the lack of clinical benefit of volatile anesthetics in some patients during cardiac surgery. This contention was confirmed by our studies conducted in several animal models of diabetes and hyperglycemia and in clinical studies. As a consequence of these initial findings, we further focused our efforts on the effects of hyperglycemia and anesthetics in regulating endothelial NO synthase and NO metabolism. Interestingly, clinical evidence was also beginning to emerge that aggressive control of blood glucose concentration may not be sufficient, or could be deleterious, to improving outcome in critically ill patients. Perhaps other strategies might be required to rescue cardioprotection produced by anesthetics or ischemic preconditioning during hyperglycemia and diabetes. For example, use of statin drugs had improved outcome in high-risk patients undergoing vascular surgery; and many of these patients had diabetes. Remarkably, the statin drug simvastatin restored anesthetic and ischemic preconditioning, despite the presence of acute hyperglycemia, this action was mediated by an NO pathway. Our laboratory is continuing to explore the intracellular regulation of enzymes involved in NO metabolism and how proteins involved in NO biosynthesis are favorably or unfavorably modulated by anesthetics and hyperglycemia, respectively. These investigations may uncover new therapeutic targets for intervention in an ever-growing population of patients with diabetes and glucose intolerance. Strategies such as the use of volatile anesthetics for myocardial protection, although widely used during cardiac surgery, may be insufficient as the sole approach to substantially improving long-term outcome in patients with coexisting diseases.

Thus, the field of anesthetic preconditioning illustrates the concept of translational research: from bench to bedside and back again, an anesthesiologist’s tale, and that of a team of investigators at the Medical College of Wisconsin.

Michelle Larcheid, B.A. (Administrative Assistant, Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, Wisconsin), is thanked for manuscript preparation.

References