

Classic Papers Revisited: An Early Study of Cardioprotection by Volatile Anesthetics

A Behind-the-scenes Look

David C. Warltier, M.D., Ph.D., F.A.H.A., F.A.C.C.

Recovery of Contractile Function of Stunned Myocardium in Chronically Instrumented Dogs Is Enhanced by Halothane or Isoflurane. By Warltier DC, al-Wathiqui MH, Kampine JP, and Schmeling WT. *ANESTHESIOLOGY* 1988; 69:552–65. Reprinted with permission.

Abstract: Following brief periods (5–15 min) of total coronary artery occlusion and subsequent reperfusion, despite an absence of tissue necrosis, a decrement in contractile function of the postischemic myocardium may nevertheless be present for prolonged periods. This has been termed “stunned” myocardium to differentiate the condition from ischemia or infarction. Because the influence of volatile anesthetics on the recovery of postischemic, reperfused myocardium has yet to be studied, the purpose of this investigation was to compare the effects of halothane and isoflurane on systemic and regional hemodynamics following a brief coronary artery occlusion and reperfusion. Nine groups comprising 79 experiments were completed in 42 chronically instrumented dogs. In awake, unanesthetized dogs a 15-min coronary artery occlusion resulted in paradoxical systolic lengthening in the ischemic zone. Following reperfusion

active systolic shortening slowly returned toward control levels but remained approximately 50% depressed from control at 5 h. In contrast, dogs anesthetized with halothane or isoflurane (2% inspired concentration) demonstrated complete recovery of function 3–5 h following reperfusion. Because the anesthetics directly depressed contractile function, additional experiments were conducted in which a 15-minute coronary artery occlusion was produced during volatile anesthesia; however, each animal was allowed to emerge from the anesthetized state at the onset of reperfusion. Similar results were obtained in these experiments, demonstrating total recovery of contractile function within 3–5 h following reperfusion. Thus, despite comparable degrees of contractile dysfunction during coronary artery occlusion in awake and anesthetized dogs, the present results demonstrate that halothane and isoflurane produce marked improvement in the recovery of segment function following a transient ischemic episode. Therefore, volatile anesthetics may attenuate postischemic left ventricular dysfunction occurring intraoperatively and enhance recovery of regional wall motion abnormalities during reperfusion.

IT is an honor for me to be requested to compose a Classic Papers Revisited article based on one of our previous investigations. For this, I travel back in time to 1988 when we published one of the first works to demonstrate that volatile anesthetics have direct cardioprotective properties (a term commonly used at present, but when the manuscript was submitted, the editor-in-chief, Lawrence J. Saidman, M.D., questioned the use of this terminology and whether “cardioprotection” was even a word).¹ At that time, I had finished my degrees in medicine and pharmacology and had interrupted further clinical training to conduct research in cardiovascular physiology, pathophysiology, and pharmacology. My laboratory was focused on myocardial ischemia and reperfusion injury and factors either deleterious or beneficial to related processes. I was lucky enough to have received grant support from the National



David C. Warltier, M.D., Ph.D., F.A.H.A., F.A.C.C., former Professor and Chairman of the Department of Anesthesiology, working at his desk at the Medical College of Wisconsin, Milwaukee, Wisconsin. Photo by Greg Diciaula, October 10, 2016.

Submitted for publication April 12, 2018. Accepted for publication May 11, 2018. From the Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, Wisconsin.

Copyright © 2018, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. All Rights Reserved. *Anesthesiology* 2018; 129:576–9



Fig. 1. I owe a great deal of thanks to John Tessmer, B.S. (*left*), and David Schwabe, B.S. (*right*), each of whom have conducted an incredible number of experiments over the last 32 yr.

Institutes of Health (Bethesda, Maryland), Veterans Administration, (Washington, DC) and American Heart Association (Dallas, Texas) for this work. We were especially interested in pharmacologic agents and established that several groups of drugs were beneficial, including beta-blocking agents, calcium antagonists, nitric oxide donors, drugs releasing oxygen from hemoglobin, or those that increase collateral perfusion to ischemic myocardium. Research in this area required a large team of talented members with multifaceted skills.

The research laboratory contained such a group of outstanding individuals with diverse backgrounds. They created an energy that permeated the laboratory. These were scientists, research technicians, biomedical engineers, postdoctoral fellows, medical students, and graduate students who came together, excited about what they were accomplishing, and moved forward the foundation of what we know about the basic science of cardioprotection. Their excitement was infectious and ignited hypothesis generation. My personal philosophy was that any research we conducted had to have potential applicability to humans and be readily publishable (today we refer to this as translational research). I wanted to develop scientists who examined cardiovascular disease and especially the effects of anesthetics on the coronary circulation.

All my mentors had an interest and passion for investigation of cardiovascular disease. Garrett J. Gross, Ph.D., professor in the Department of Pharmacology, Medical College of Wisconsin (Milwaukee, Wisconsin), taught me more about research than anyone and served as my advisor during graduate school. Harold F. Hardman, M.D., Ph.D., chairman of the Department of Pharmacology, steered my ultimate career toward

medicine, and John P. Kampine, M.D., Ph.D., chairman of the Department of Anesthesiology at the Medical College of Wisconsin, had the vision to understand that a physician scientist needed time for both research and clinical medicine.

At the time the research described in the classic article¹ was being performed, I was an associate professor with a joint appointment in the Departments of Pharmacology and Medicine (Division of Cardiology). Stimulated by the research for this investigation and the encouragement by a dear friend and coauthor of this study, William T. Schmeling, M.D., Ph.D., an assistant professor of anesthesiology and pharmacology at the Medical College of Wisconsin, I became interested in anesthesiology as a career. I began a residency program at the Medical College of Wisconsin at the further behest of John P. Kampine, M.D., Ph.D. John was a close friend, confidant, and mentor who I first met as a student in 1971. He suggested to me early on that there was a paucity of studies examining the effects of anesthetics on myocardial ischemia and infarction and the coronary circulation. He recognized the expertise of my laboratory group and suspected we could make exceptional progress in this area.

The team I had assembled in the laboratory was capable of conducting experiments in many species, including conscious, chronically instrumented dogs or those anesthetized solely with isoflurane or halothane. The core group included John Tessmer, B.S., David Schwabe, B.S. (fig. 1), Judy R. Kersten, M.D. (once a fellow and now a professor emeritus), Douglas A. Hettrick, Ph.D. (once a graduate student and now the director of medical affairs for coronary and renal denervation at Medtronic, Minneapolis, Minnesota),

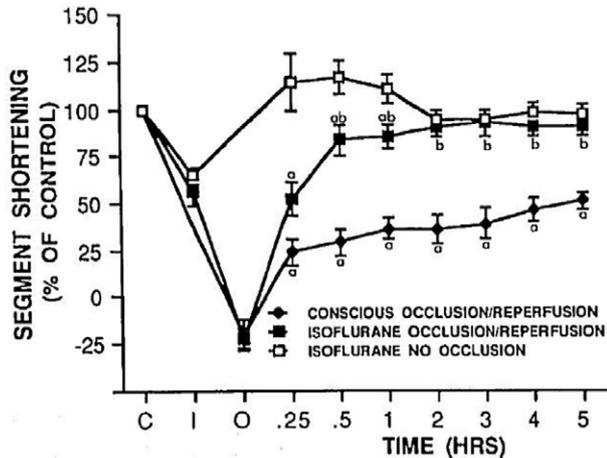


Fig. 2. Contractile function expressed as segment shortening in conscious control experiments after coronary artery occlusion and reperfusion *versus* dogs anesthetized with isoflurane during coronary occlusion. For comparison, animals exposed to isoflurane without coronary artery occlusion are included. Reprinted with permission from ANESTHESIOLOGY 1988; 69:552–65 (fig. 5 in original article; legend edited from original).

J. Craig Hartman, Ph.D. (once a graduate student and now vice president of Pharmacology and Preclinical Development at Revivo Therapeutics, Durham, North Carolina), from the Medical College of Wisconsin, and a host of others over the next 37 yr. Typical instrumentation for experiments included aortic and right atrial catheters, a left ventricular miniature micromanometer, ultrasonic myocardial segment length gauges, coronary flow transducers, and a coronary artery balloon cuff occluder. Many of these devices were constructed in the laboratory. All were implanted under sterile conditions, and the animals were allowed to recover over 7 to 10 days. The actions of any drug including an anesthetic agent could be directly compared to the conscious, unsedated state without the complicating, nonspecific effects of a baseline anesthetic. Few laboratories in the world had the capability of conducting such a study or the personnel to do it. Because no baseline anesthetic such as pentobarbital was required in this model, the pure effect of the anesthetic to be studied could be established. Studies comparing two anesthetics without a conscious control must be interpreted with great caution.

And so, this investigation was an initial foray into the impact of volatile anesthetics, including isoflurane, on myocardial ischemia and reperfusion injury. We decided to examine their effects on myocardial stunning. Interruption of perfusion to myocardium for a brief period results in aneurysmal bulging of the affected myocardial segment; but with restoration of coronary flow, mechanical function does not immediately return to normal. Only after hours to days does contractility return to preocclusion levels. Myocardium acts as if it were temporarily stunned.² This form of myocardial injury was selected for study because it was less severe than the irreversible tissue damage produced in myocardial infarction. The key decision in choosing this model was that the

ischemic injury was not so severe that no agent could possibly produce a beneficial effect. The injury also needed to be of appropriate severity to determine if an anesthetic such as isoflurane could exacerbate the injury. Injury of intermediate severity allowed us to determine either a beneficial or deleterious action of the volatile agent.

At the time our study was conducted, the use of isoflurane in patients with coronary artery disease was at best felt to be controversial and at worst, absolutely dangerous.^{3,4} Isoflurane was thought to produce coronary steal secondary to its coronary vasodilator properties.^{3,5} Coronary steal was defined as a reduction in collateral perfusion to an ischemic zone distal to a coronary artery occlusion during an increase in perfusion to normal areas.^{5–7} This theoretically would intensify myocardial ischemia, and an increased delay in return of normal contractile function of stunned myocardium would be expected to occur during reperfusion.

We compared the effects of halothane and isoflurane on recovery of mechanical function of myocardium after a brief coronary artery occlusion and reperfusion that produced stunning but was insufficient to produce infarction in chronically instrumented dogs.¹ In control dogs not exposed to a volatile agent, contractile performance at 5 h following reperfusion after a 15-min coronary occlusion was approximately 50% of normal. In dogs exposed to isoflurane during coronary artery occlusion and then allowed to emerge from anesthesia coincident with reperfusion, recovery from stunning was observed as early as 30 min after the onset of reperfusion, and return to normal levels was extremely rapid (fig. 2). Halothane caused similar effects. Both anesthetics produced marked improvement in recovery of contractile function after a transient ischemic episode. Remarkably, isoflurane was just as effective as halothane. Although we did not measure myocardial oxygen consumption, this action appeared independent of the major hemodynamic determinants of myocardial oxygen demand.

These beneficial effects of a previous exposure of the volatile anesthetics despite their subsequent absence prompted us to examine their action in more detail in many subsequent studies. If isoflurane had produced a steal of perfusion away from the ischemic zone, the stunning would be expected to be more severe and last for a longer time. Halothane, which has no coronary vasodilator properties, would not be expected to produce steal, and as a consequence, myocardial stunning would be expected to be less with halothane than with isoflurane. These were not the results we observed. In fact, both volatile anesthetics reduced stunning of postischemic, reperfused myocardium.

We did not recognize it at the time, but we had obtained the very first evidence of pharmacologic preconditioning by a volatile anesthetic. Great science is conducted by those who keep an open mind, but at times, intense focus on the work can lead to myopia. We simply were wearing blinders and did not consider until much later that anesthetics could have this activity. This was especially fascinating as we were examining preconditioning in experiments with other drugs.

In later experiments, we repeated the work with volatile agents in barbiturate-anesthetized dogs undergoing multiple coronary artery occlusions and reperfusion.⁸ Once again, animals exposed to isoflurane had dramatic recovery of function. The unusual feature of this action was the characteristic of “memory.” The volatile anesthetic could be eliminated, yet the cardioprotective effect remained for a long duration. Myocardium acted as if it “recalled” the previous anesthetic exposure, a key feature analogous to a brief period of ischemia preceding a prolonged coronary occlusion in ischemic preconditioning,⁹ also referred to as “memory.”

The results were unexpected and exciting on two fronts. First, they led us to conduct further investigations of isoflurane on myocardial blood flow distal to a coronary artery stenosis and/or a total coronary artery occlusion to directly assess the impact of isoflurane on coronary steal.^{6,7} Second, we hypothesized that isoflurane may mimic ischemic preconditioning and have direct, beneficial cardioprotective properties independent of any hemodynamic effect. These complex investigations conducted in multiple species including chronically instrumented dogs were completed over the next several years and demonstrated that isoflurane did not have the coronary vasodilator efficacy¹⁰ to produce a steal of perfusion away from ischemic myocardium. This was in direct contrast to a potent vasodilator, adenosine, used as a positive control for comparison.⁷ On the other hand, if isoflurane decreased arterial pressure and thus driving pressure for collateral perfusion, blood flow to the ischemic zone was reduced. This nonspecific action, caused by any means that reduces arterial pressure, needed to be controlled in our experiments. Also, the initial study¹ and others like them on myocardial stunning compelled us to further examine the direct action of volatile anesthetics to precondition myocardium against an ischemia and reperfusion injury of greater severity. In fact, the volatile anesthetics, including isoflurane, mimicked ischemic preconditioning, and we determined a portion of the mechanism whereby they acted in this manner: through activation of adenosine-triphosphate-regulated potassium channels.^{8,11} These experiments opened a fascinating new area of investigation in anesthesiology, cardioprotection by volatile anesthetics, which was pursued by our laboratory and many others.^{12–14}

Correspondence

Address correspondence to Dr. Wartier: Department of Anesthesiology, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, Wisconsin 53226. wartier@mcw.edu.

Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

References

1. Wartier DC, al-Wathiqui MH, Kampine JP, Schmeling WT: Recovery of contractile function of stunned myocardium in chronically instrumented dogs is enhanced by halothane or isoflurane. ANESTHESIOLOGY 1988; 69:552–65
2. Braunwald E, Kloner RA: The stunned myocardium: Prolonged, postischemic ventricular dysfunction. Circulation 1982; 66:1146–9
3. Reiz S, Bålfors E, Sørensen MB, Ariola S Jr, Friedman A, Truedsson H: Isoflurane—a powerful coronary vasodilator in patients with coronary artery disease. ANESTHESIOLOGY 1983; 59:91–7
4. Reiz S, Ostman M: Regional coronary hemodynamics during isoflurane-nitrous oxide anesthesia in patients with ischemic heart disease. Anesth Analg 1985; 64:570–6
5. Buffington CW, Romson JL, Levine A, Duttlinger NC, Huang AH: Isoflurane induces coronary steal in a canine model of chronic coronary occlusion. ANESTHESIOLOGY 1987; 66:280–92
6. Hartman JC, Kampine JP, Schmeling WT, Wartier DC: Alterations in collateral blood flow produced by isoflurane in a chronically instrumented canine model of multivessel coronary artery disease. ANESTHESIOLOGY 1991; 74:120–33
7. Hartman JC, Kampine JP, Schmeling WT, Wartier DC: Steal-prone coronary circulation in chronically instrumented dogs: Isoflurane *versus* adenosine. ANESTHESIOLOGY 1991; 74:744–56
8. Kersten JR, Schmeling TJ, Pagel PS, Gross GJ, Wartier DC: Isoflurane mimics ischemic preconditioning via activation of K(ATP) channels: Reduction of myocardial infarct size with an acute memory phase. ANESTHESIOLOGY 1997; 87:361–70
9. Murry CE, Jennings RB, Reimer KA: Preconditioning with ischemia: A delay of lethal cell injury in ischemic myocardium. Circulation 1986; 74:1124–36
10. Kenny D, Proctor LT, Schmeling WT, Kampine JP, Wartier DC: Isoflurane causes only minimal increases in coronary blood flow independent of oxygen demand. ANESTHESIOLOGY 1991; 75:640–9
11. Kersten JR, Schmeling TJ, Hettrick DA, Pagel PS, Gross GJ, Wartier DC: Mechanism of myocardial protection by isoflurane. Role of adenosine triphosphate-regulated potassium (KATP) channels. ANESTHESIOLOGY 1996; 85:794–807; discussion 27A
12. Frässdorf J, De Hert S, Schlack W: Anaesthesia and myocardial ischaemia/reperfusion injury. Br J Anaesth 2009; 103:89–98
13. Lucchinetti E, Hofer C, Bestmann L, Hersberger M, Feng J, Zhu M, Furrer L, Schaub MC, Tavakoli R, Genoni M, Zollinger A, Zaugg M: Gene regulatory control of myocardial energy metabolism predicts postoperative cardiac function in patients undergoing off-pump coronary artery bypass graft surgery: Inhalational *versus* intravenous anesthetics. ANESTHESIOLOGY 2007; 106:444–57
14. De Hert SG, Turani F, Mathur S, Stowe DF: Cardioprotection with volatile anesthetics: Mechanisms and clinical implications. Anesth Analg 2005; 100:1584–93