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Editorial View

Anesthetic Preconditioning: Serendipity and Science

In this issue of ANESTHESIOLOGY, we are doing something different. Over the past several years, we have published a great many articles on anesthetic preconditioning of the heart. It is clear that more and more anesthesiologists, both clinicians and laboratory investigators, are now working in this area. By chance, seven of these articles emerged from the peer-review process at approximately the same time. Since this is an area of growing importance, and since we are just now beginning to see the application of laboratory science to the clinical arena (see the article by De Hert *et al.*), I feel it is appropriate to highlight these articles by setting them aside in a special section of the Journal.

I also asked one of our editors, Dr. Warltier, to author an Editorial View along with several of his colleagues from the Medical College of Wisconsin. These editorialists have been among the most productive individuals in the field and have made major contributions (many of which have appeared in ANESTHESIOLOGY). I fully realize that two of the articles included in this special section originate at their own institution—in fact, they come from their own department. While this may appear to be a serious conflict of interest, I cannot think of any group more qualified to write such an Editorial View than Drs. Warltier, Kersten, Pagel, and Gross.

Stay tuned. These clearly will not be the last articles on this subject. There is a very real potential that anesthetic agents may soon be recognized as having a direct therapeutic effect in patients undergoing cardiac surgery. That should be of interest to all anesthesiologists.

Michael M. Todd, M.D., Editor-in-Chief, anesthesiology@uiowa.edu

THIS issue of the Journal contains a special section devoted to a series of articles[1–7] addressing pharmacological preconditioning of myocardium by volatile anesthetics. These articles represent only a small fraction of the recent publications related to the subject of anesthetic preconditioning (APC). In fact, since 1999, ANESTHESIOLOGY has published more than 20 investigations on this phenomenon. This year's June and July issues of the *American Journal of Physiology-Heart and Circulatory Physiology* contained special sections on pharmacological preconditioning, and the 2003 American Society of Anesthesiologists Annual Meeting Journal Symposium will feature the topic of APC.

This Editorial View accompanies the following seven articles: Zaugg M, Lucchinetti E, Spahn DR, Pasch T, Schaub MC: Volatile anesthetics mimic cardiac preconditioning by priming the activation of mitoK$_{ATP}$ channels *via* multiple signaling pathways. ANESTHESIOLOGY 2002; 97:4–14; Zaugg M, Lucchinetti E, Spahn DR, Pasch T, Garcia C, Schaub MC: Differential effects of anesthetics on mitochondrial K$_{ATP}$ channel activity and cardiomyocyte protection. ANESTHESIOLOGY 2002; 97:15–23; de Klaver MJM, Manning L, Palmer LA, Rich GF: Isoflurane pretreatment inhibits cytokine-induced cell death in cultured rat smooth muscle cells and human endothelial cells. ANESTHESIOLOGY 2002; 97:24–32; Hanouz JL, Yvon A, Massetti M, Lepage O, Babatasi G, Khayat A, Bricard H, Gerard JL: Mechanisms of desflurane-induced preconditioning in isolated human right atria *in vitro*. ANESTHESIOLOGY 2002; 97:33–41; De Hert SG, ten Broecke PW, Mertens E, Van Sommeren EW, De Blier IG, Stockman BA, Rodrigus IE: Sevoflurane but not propofol preserves myocardial function in coronary surgery patients. ANESTHESIOLOGY 2002; 97:42–9; Kwok WM, Martinelli AT, Fujimoto K, Suzuki A, Stadnicka A, Bosnjak ZJ: Differential modulation of the cardiac ATP-sensitive potassium channel by volatile anesthetics. ANESTHESIOLOGY 2002; 97:50–6; Fujimoto K, Bosnjak ZJ, Kwok WM: Isoflurane-induced facilitation of the cardiac sarcolemmal K$_{ATP}$ channel. ANESTHESIOLOGY 2002; 97:57–65.

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Personal Observations

Over the past few years, both serendipity and scientific investigation have revealed that volatile agents may have important cardioprotective properties against myocardial ischemia and reperfusion injury. The findings may ultimately have an impact on the practice of anesthesia for patients with coronary artery disease. Several research laboratories were initially involved in studies of the coronary collateral circulation in animals following reports that coronary steal could produce myocardial ischemia during administration of isoflurane to patients with coronary artery disease. A series of investigations in experimental animals found that this was not the case, and, in fact, the opposite was true—volatile anesthetics have cardioprotective properties.[8] Protection against reversible and irreversible myocardial injury by these agents was not easily explained by simple alterations in myocardial oxygen supply and demand. In contrast, previous clinical investigations had not found evidence to suggest that one anesthetic technique was preferable to another for patients with coronary artery disease. Thus, early laboratory findings went largely unresolved with the appearance of having few if any direct implications for administration of volatile anesthetics to humans.

More recently, medical economics has driven anesthesiologists to assist in reducing healthcare costs by tailoring anesthetics to allow shorter lengths of stay, especially in high-cost centers, such as intensive and postanesthesia care units. Remarkably, instead of scientific investigation guiding decisions as to which anesthet-

ics or techniques to use for improved outcome, shorter-acting drugs that allow patients to be extubated earlier, leave the intensive care unit sooner, and be discharged from the hospital more rapidly are advocated. This resulted in a change from what was largely a high-dose opioid technique to, instead, a primarily volatile anesthetic technique for patients undergoing coronary artery bypass graft surgery. As anesthesia for cardiac surgery changed, more than a few of the authors' colleagues at this institution and others have suggested that fewer intraoperative ischemic events may be observed in this patient population. Other anesthesiologists have commented that in their practice, the need for pharmacological or mechanical circulatory support was less frequent after revascularization. The reasons for these anecdotal observations are probably multifactorial. Many fundamental changes in the approach to the patient undergoing coronary artery bypass graft surgery have occurred, and only a few are related to the type of anesthetic delivered. Nevertheless, it is possible that economic pressures led to a relatively greater use of volatile anesthetics in patients undergoing cardiac surgery, and this resulted in a reduced frequency of ischemic events because these agents possess cardioprotective properties. Serendipity may have allowed for this as yet untested observation in humans, which was simultaneously being intensively studied in the basic research laboratory.

Ischemic Preconditioning

Laboratory and clinical investigations have demonstrated that single or multiple brief periods of ischemia are not necessarily deleterious and, instead, can be protective against a subsequent prolonged ischemic insult. The brief periods of ischemia appear to "precondition" myocardium against reversible or irreversible tissue injury, including stunning, infarction, and the development of malignant ventricular arrhythmias. This process, termed ischemic preconditioning (IPC), results in finite periods in which the myocardium is protected following a brief period of ischemia. An early phase or window of IPC persists for 1 to 2 h before "disappearing" and then reoccurring 24 h later. This second or late window of preconditioning may last for as long as 3 days.

Ischemic preconditioning is a fundamental endogenous protective mechanism against tissue injury ubiquitous to all species in which it has been studied. IPC is best characterized in the heart, but it is also present in other tissues. The mechanism(s) whereby IPC reduces the extent of myocardial infarction have been extensively studied over the past few years. A variety of ligands and multiple receptors coupled to G proteins are primarily responsible for activation of an intracellular signal transduction pathway that involves protein kinase C, mitogen-activated protein kinases, protein tyrosine kinases, reactive oxygen species, and nitric oxide synthase. Central to this process is the role of the mitochondrial adenosine triphosphate–sensitive potassium (K_{ATP}) channel. Opening of this channel is critical for the beneficial cardioprotective effects of IPC. As the components involved in the intracellular signal transduction pathway of IPC have been better defined, pharmacological agonists and antagonists of various mediators have been tested in an effort to develop new therapeutic agents that might also precondition myocardium. During this time, the beneficial effects of volatile anesthetics against ischemic injury have been revisited, IPC providing a strong stimulus to evaluate mechanisms of APC.

Anesthetic Preconditioning

The inability to relate the antiischemic effects of volatile anesthetics to improvement of myocardial oxygen supply–demand balance led to the concept that these agents may have direct cardioprotective properties.[9] Volatile anesthetics have been shown to directly precondition[10,11] or indirectly enhance IPC, resulting in cardioprotection against myocardial infarction with the K_{ATP} channel playing an important role.[10] Pharmacological preconditioning produced by volatile agents, including isoflurane, desflurane, and sevoflurane, is remarkably similar to IPC and shares many of the same signal transduction elements. Further mechanisms of action are now being explored.

In this issue of the Journal, Zaugg *et al.*[1,2] provide additional evidence that mitochondrial K_{ATP} channels are critical to APC by volatile agents and also demonstrate that certain intravenous anesthetics may have deleterious effects on preconditioning produced by K_{ATP} channel openers. Cardiac sarcolemmal K_{ATP} channels may also be modulated by volatile anesthetics. Kwok *et al.*[3] demonstrate that isoflurane may not directly alter sarcolemmal K_{ATP} channels but instead potentiates opening of the channel by other agonists. Other results from this laboratory show that the action of isoflurane on the K_{ATP} channel requires endogenous mediators, most likely PKC.[4] Thus, alterations in intracellular kinases, such as PKC, may be involved in APC,[1,5] and the work of de Klaver *et al.*[5] suggests that APC is not limited to cardiomyocytes, but protection against vascular smooth muscle and endothelial cell death by isoflurane and halothane is also possible. Hanouz *et al.*[6] confirm that desflurane is cardioprotective, and this agent may act *via* multiple mechanisms that ultimately converge on the mitochondrial K_{ATP} channel. These investigators further demonstrate that adenosine and α- and β-adrenergic receptors may also be involved in APC signal transduction.

Finally, in this issue of the Journal a small clinical investigation by De Hert *et al.*[7] has suggested that volatile anesthetics are cardioprotective in humans. This

study demonstrates that sevoflurane-anesthetized patients had reduced cardiac enzyme release and improved left ventricular function after coronary artery bypass graft surgery as compared to patients anesthetized with propofol. This and several other initial clinical studies[12–14] are extraordinarily provocative. Larger investigations of the impact of volatile anesthetics, including cardiac morbidity (*e.g.*, frequency of myocardial infarction) and mortality using many centers and thousands of patients, are now required to further establish the clinical significance of APC in humans. Experimental results to date demonstrating the existence and mechanisms of APC and preliminary clinical evidence suggesting that APC also occurs in humans warrant such multicenter trials.

David C. Warltier, M.D., Ph.D.,* Judy R. Kersten, M.D.,† Paul S. Pagel, M.D., Ph.D.,‡ Garrett J. Gross, Ph.D.§ *Professor and Vice Chairman for Research, Departments of Anesthesiology, Pharmacology and Toxicology, and Medicine (Division of Cardiovascular Diseases), the Medical College of Wisconsin, Milwaukee, Wisconsin, and the Clement J. Zablocki Veterans Affairs Medical Center, Milwaukee, Wisconsin. †Departments of Anesthesiology and Pharmacology and Toxicology, §Department of Pharmacology and Toxicology, the Medical College of Wisconsin. ‡Department of Anesthesiology, the Medical College of Wisconsin, and the Clement J. Zablocki Veterans Affairs Medical Center. cknapp@mcw.edu

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