Cardiac pharmacological preconditioning with volatile anesthetics: from bench to bedside?

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Reperfusion after myocardial ischemia can result in stunning that may be reversible with time or lead to irreversible tissue damage. Noncardiac surgery poses a risk for patients with coronary artery disease to develop perioperative myocardial infarction (2). In addition, myocardial ischemia is frequently induced during cardiac procedures such as coronary angiography, angioplasty, cardiac valve replacement, and coronary artery bypass grafting and is a necessary consequence of heart transplantation.

Many approaches and therapies focus on reducing the incidence of perioperative ischemia and its deleterious effects. Volatile anesthetics are commonly used for general anesthesia during surgery to induce and maintain hypnosis, analgesia, and amnesia and to produce mild muscle relaxation. Previous clinical investigations had not found any strong evidence that one anesthetic was preferable to another for patients with coronary artery disease or that the selection of a volatile anesthetic would significantly increase morbidity or mortality (51, 64). However, during the study of their cardiovascular effects to decrease cardiac contractility and reduce vascular resistance (15), volatile anesthetics were found in the 1980s to enhance tolerance to myocardial ischemia (58) and to improve posts ischemic recovery in isolated hearts (11) as well as in vivo (67). Since these early discoveries, more investigations have shown that volatile anesthetics enhance posts ischemic mechanical function and reduce infarction in various animal models independent of changes in myocardial oxygen supply and demand (for reviews, see Refs. 7, 47, 53, 55, and 73). It is now well accepted that these agents produce pharmacological preconditioning. The purpose of this minireview is to provide a succinct overview of the basic research on cardioprotection by volatile anesthetics and how this may translate into clinical practice.

Phenomenon of Preconditioning

In 1986, Murry et al. (37) found that four cycles of 5-min left circumflex coronary artery occlusions, before a 40-min occlusion, reduced myocardial infarction by 75%. This phenomenon was named “ischemic preconditioning” and has been extensively investigated. In principle, the preconditioning stimuli of short ischemia and reperfusion trigger a signaling cascade of intracellular events and thus create a memory effect that attenuates ischemia-reperfusion injury. These signals are thought to include release or activation of mediators like adenosine, bradykinin, opioids, norepinephrine, free radicals, inhibitory guanine nucleotide binding proteins, and PKC; eventually, sarcolemmal and mitochondrial ATP-sensitive K+ channels (KATP channels) are thought to be activated and confer cardioprotection during ischemia and reperfusion.

The cardioprotection of the classic or early preconditioning lasts for 2 to 3 h. A second window of protection (late preconditioning) appears after 12 to 24 h and lasts up to 72 h (29). In contrast to early preconditioning, late preconditioning depends on gene transcription and de novo protein synthesis. For detailed reviews on ischemic preconditioning, see Refs. 40, 68, and 73.

Ischemic preconditioning has also been described in organs other than the heart, including the brain (for a review, see Ref. 8), kidney (for a review, see Ref. 4), and liver (for a review, see Ref. 27). Ischemic preconditioning is not only a laboratory phenomenon but also occurs clinically in humans. For exam-
ple, patients who experience prodromal symptoms of myocardial angina within 24 h before subsequent acute myocardial infarction demonstrate a more rapid recovery and improved survival (16). However, to protect a patient’s heart against injury by possible or planned ischemia and reperfusion, inducing preconditioning by pharmacological means seems more applicable. Volatile anesthetics have been successfully used in patients for decades and may offer a useful role in patients with coronary artery disease undergoing surgery.

**Anesthetic Preconditioning**

In a fashion similar to ischemic preconditioning, volatile anesthetics can trigger an acute cardioprotective memory effect that lasts beyond their elimination (5, 6, 23). This early preconditioning has been prevented by adenosine A1 receptor antagonists (46), G protein inhibitors (61), reactive oxygen species scavengers (25, 36, 39, 57), PKC inhibitors (6, 38, 62, 65), KATP channel blockers (23, 41, 45, 46, 60, 69), and cyclooxygenase type 2 inhibitors (35). Although the exact signaling pathway is not yet fully understood, all of these observations suggest that volatile anesthetics precondition the myocardium by mechanisms similar to ischemic preconditioning but they have the distinct advantage of not requiring ischemia to produce this effect. Volatile anesthetics are lipophilic and can easily diffuse through cellular and subcellular membranes. They do not require ionic or covalent binding to specific receptors but can interact with lipophilic amino acids to cause conformational changes in membranes, channels, and enzymes (10). In this way, like other lipophilic drugs (28, 34), they can alter mitochondrial electron transport (26, 43, 45). This is thought to cause enhanced electron leakage and reactive oxygen species generation, which may act as a trigger for preconditioning (25, 36, 39, 57) and lead to PKC activation (38), KATP channel opening (30, 72), and differential gene regulation (70). For more detailed reviews on mechanisms of anesthetic preconditioning, see Refs. 7, 47, 53, 55, 71, and 73. By conferring protection to the myocardium as well as to other tissues (18, 33) beyond the duration of the anesthetic exposure during anesthesia, anesthetic preconditioning may offer additional benefits during the vulnerable postoperative period.

**Preconditioning of the Aged Heart**

The majority of research into cardioprotective measurements involves models using younger animals. Interestingly, cardioprotective strategies would be most beneficial for the middle-aged and elderly. Tolerance to stress in older animals is generally lower than that in younger animals, and most cardiac complications in humans occur later in life. Therefore, preconditioning of the aged myocardium is an important issue that may differ considerably from preconditioning of myocardium in the younger so that cardioprotection may need to be tailored to the aged population (for a review, see Ref. 59). Some investigators have found that age does not influence the myocardial tolerance to ischemia or the protective effect of ischemic preconditioning (31), whereas other studies question the ability of aged myocardium to be susceptible to preconditioning at all (1). Schulman et al. (49), for example, reported that aged rat hearts could not be preconditioned by ischemic or pharmacological means and that middle-aged rat hearts had only a blunted response to preconditioning compared with young adult hearts. They suggested defects within the signaling cascade of preconditioning in the aged heart. Evidence from an isolated heart model points in the same direction for anesthetic preconditioning, suggesting that the benefits of anesthetic preconditioning may indeed be reduced with advanced age (52). In any case, the role of pharmacological and anesthetic preconditioning in aged hearts needs to be thoroughly investigated before any conclusion can be drawn as to its applicability in the clinical situation.

**Preconditioning and Diabetes Mellitus**

Acute and chronic hyperglycemia increases the risk for cardiac ischemic injury. Endogenous protective signaling pathways are impaired, and coronary blood flow to the ischemic myocardium is reduced during hyperglycemia. Despite the experimental evidence that hyperglycemia adversely alters cardiac signal transduction and impairs regulation of coronary hemodynamics, no clinical trial has been conducted so far to modify the perioperative cardiovascular risk in diabetic patients. Nevertheless, perioperative blood glucose control may prove beneficial (for a review, see Ref. 14).

Adequacy of control of blood glucose concentration will affect anesthetic preconditioning. High blood glucose concentrations have been shown to antagonize ischemic and anesthetic preconditioning in the presence and absence of diabetes in different animal models (9, 19, 22, 54). Even if adult-onset diabetes mellitus is successfully treated, in part or solely, by sulfonylurea oral hypoglycemic drugs such as glibenclamide, patients will most likely not benefit from any form of preconditioning. The target of sulfonylurea drugs is the KATP channel in the pancreatic B-cell: closure of the KATP channel causes insulin release. KATP channels are also present in sarcolemmal and possibly in mitochondrial membranes of cardiac myocytes (13). Their activation has been implicated as both a trigger and effector of myocardial preconditioning, and both ischemic and anesthetic preconditioning are abolished by sulfonylurea drugs. Oral hypoglycemic agents should therefore be discontinued 24 to 48 h before elective surgery. Instead, insulin should be used to maintain normoglycemia. Insulin has the added benefit of activating cell survival pathways, including the phosphatidylinositol 3′-kinase/Akt-dependent pathway to decrease infarct size and apoptotic myocyte death (12).

**Timing and Duration of Ischemia**

To demonstrate the beneficial effects of anesthetic preconditioning and to study the signal transduction pathways involved, investigators have to select a specific duration of ischemia that varies among models and species. If the ischemia is too short, the damage is not serious enough to be attenuated by preconditioning. If the ischemia is too long, preconditioning is not powerful enough to improve the outcome. Kevin et al. (24) in a recent study in isolated hearts found an optimal effect of anesthetic preconditioning only for a limited ischemia duration of ~25 min. They also showed that preconditioned hearts only tolerate ischemia ~10 min longer than nonpreconditioned hearts to result in the same tissue damage. However, coronary perfusion was better maintained after preconditioning for up to 45 min ischemia suggesting better preservation of vascular than mechanical function. Thus it appears that only when the duration of ischemia falls within a certain window...
does the myocardium benefit from preconditioning. Varying tolerance to ischemia among different species (50) may alter the duration of this window and further complicate transferability of results from animal studies to the clinical situation.

Another issue is that the cardioprotective effects of anesthetic and other forms of pharmacological preconditioning last only for a limited time after the preconditioning stimulus, i.e., a first window. Patients with coronary artery disease undergoing noncardiac surgery, however, have the greatest severity of perioperative myocardial ischemia at times over 24 h postoperatively (32). In this context, a second window of anesthetic preconditioning after 24 h, as reported for ischemic preconditioning, would certainly be beneficial in the clinical setting. However, studies on whether a second window of anesthetic preconditioning exists (similar to ischemic preconditioning) have furnished inconsistent results (21, 56, 63).

Application

Cardioprotection by anesthetic preconditioning may have important implications in the clinical setting. One is cardioprotection against possible ischemia during the perioperative period in patients with coronary artery disease undergoing noncardiac surgery. The other is protection against the myocardial ischemia expected to occur during cardiac surgery or coronary angioplasty.

The question at hand for the clinician is how anesthetic preconditioning can be best achieved in the clinical setting. A supraclinical concentration (four minimal alveolar concentrations [MAC] sevoflurane) led to a better cardioprotection than a lower concentration (2 MAC) as shown by postischemic function and infarct size in an isolated heart model (42). Transferring these results into clinical practice, however, is limited by the marked cardiodepressant side effects of such a high concentration, especially when treating patients who already have impaired cardiac function. Whether anesthetic preconditioning is dose dependent in vivo and within the range of clinically applicable concentrations has not yet been fully elucidated (20).

At least for ischemic preconditioning, several cycles of preconditioning have been shown to improve outcome compared with only one cycle (48), suggesting greater accumulation of critical mediators of preconditioning with each cycle. It is unclear whether anesthetic preconditioning can be enhanced by administering the volatile anesthetic in several cycles of exposure interspersed with its washout. So far, data from an isolated heart model suggest that this may be the case (44), but no in vivo study has been conducted yet to support this evidence. If repeated washout of the anesthetic proves critical to improving anesthetic preconditioning at clinically relevant concentrations, allowing enough time for sufficient washout to occur in vivo may be severely constrained by practical considerations during anesthesia and surgery.

Clinical Studies

Because of obvious limitations it has been difficult in the past to provide sufficient evidence for anesthetic preconditioning in clinical studies. A few clinical studies with a small number of patients have been conducted, with somewhat limited success. The beneficial effects of volatile anesthetics in elderly high-risk patients undergoing elective coronary artery bypass grafting have so far been confined to surrogate markers. In a study by Belhomme et al. (3) on patients age 70 ± 9 yr undergoing elective coronary artery bypass grafting, anesthetic preconditioning was elicited after the onset of cardiopulmonary bypass by a 5-min exposure to 2.5 MAC isoflurane, followed by a 10-min washout before aortic cross-clamping and cardiopulmonary arrest. The authors found a smaller release of troponin I and creatine kinase-MB. Julier et al. (17) preconditioned with 2 MAC sevoflurane during the first 10 min of cardiopulmonary bypass and found a decreased release of brain natriuretic peptide postoperatively compared with control patients. Perioperative ST segment changes, frequency of dysrhythmias, and creatine kinase-MB or cardiac troponin release were not different between groups. Van Der Linden et al. (66) investigated the effects of several anesthetics on recovery of myocardial function in coronary surgery patients older than 70 yr with three-vessel disease and an ejection fraction <50%. The volatile anesthetics sevoflurane and desflurane preserved left ventricular function after surgery with less evidence of myocardial damage postoperatively (66). Although these results suggest a beneficial effect of cardioprotection and preconditioning by volatile anesthetics in elderly patients with coronary artery disease, no clinical investigation to date has shown decreased long-term morbidity and mortality by anesthetic preconditioning.

In conclusion, a steadily increasing number of nonclinical investigations demonstrate that preconditioning with volatile anesthetics can attenuate myocardial ischemia and reperfusion injury. Protection by volatile anesthetics is likely afforded by an ischemic preconditioning-like effect as they appear to reversibly alter mitochondrial function, a major factor in inducing preconditioning. Volatile anesthetics are easily eliminated from the body and cause no lasting deleterious effect. Thus volatile anesthetics are likely a good choice for anesthesia in patients at risk for myocardial ischemia. However, factors such as old age, coexisting disease, the use of oral sulfonylurea drugs or cyclooxygenase 2 inhibitors, timing and duration of myocardial ischemia, and practical constraints of a possibly complicated preconditioning protocol may limit the benefits of these drugs under clinical conditions. Well-planned multicenter clinical studies are needed to transfer the results of basic research into clinical practice.

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