A Recipe for Perioperative Cardioprotection
What Matters Most? The Ingredients or the Chef?

Judy R. Kersten, MD

The question of what is the ideal anesthetic for patients with cardiovascular disease has been debated for nearly 3 decades, and, similar to the case for the use of perioperative β-blockers, the answer appears to be increasingly enigmatic. In the current issue of Circulation, Buse et al report the results of a randomized clinical trial to evaluate the effects of the volatile anesthetic sevoflurane versus the intravenous anesthetic propofol on the incidence of myocardial ischemia in 385 patients with known coronary artery disease or with ≥2 risk factors for coronary artery disease undergoing noncardiac surgery. Using continuous electrocardiography and troponin T plasma concentrations as the composite primary end point of the study, the incidence of myocardial ischemia was similar in both groups (sevoflurane, 40.8%; propofol, 40.3%), calling into question the current American College of Cardiology/American Heart Association guidelines recommending the use of volatile anesthetics for patients at cardiovascular risk who are undergoing noncardiac surgery.

In the mid-1980s, volatile anesthetic agents, particularly isoflurane, were shunned by cardiac anesthesiologists for fear that these agents might induce myocardial ischemia because of coronary steal. High-dose opioids were favored as an alternative technique during anesthesia for cardiac surgery. The myth of isoflurane-induced steal was later debunked both by animal studies and clinical trial data. By the early 1990s, volatile anesthetic use during cardiac surgery had gained considerable popularity, primarily because it allowed patients to be fast-tracked for early extubation within hours of arrival to the intensive care unit as compared with opioid-based anesthetics. In 1997, the phenomenon of anesthetic preconditioning was first described, and subsequently a large body of experimental evidence demonstrated the cardioprotective effects and signaling pathways involved in early and late anesthetic preconditioning, as well as anesthetic postconditioning. These findings were confirmed in patients undergoing coronary artery bypass graft surgery; however, conflicting data regarding the beneficial effects of volatile anesthetics to decrease troponin concentrations compared with intravenous techniques after cardiac surgery have been reported recently. Evidence to support or refute the anti-ischemic effects of volatile anesthetics in noncardiac surgery, where the risk of myocardial ischemia is less predictable or in which anesthetics are specifically used to precondition or postcondition the heart, have been scant.

The findings reported by Buse et al provoke the questions, “Are volatile anesthetic agents cardioprotective in noncardiac surgery?” and “Does anesthetic choice matter?” Volatile anesthetics have been shown to precondition and postcondition myocardium through a variety of signaling molecules and proteins, including endothelial nitric oxide synthase, heat shock protein 90, tetrahydrobiopterin, mitochondrial and sarcolemmal adenosine triphosphate-regulated potassium channels, intracellular survival kinases, and membrane-bound receptors. The timing and mode of administration (stuttered versus continuous), as well as the dose of volatile anesthetic, influences the efficacy of these drugs to reduce ischemic injury. In addition, opioids that are routinely used in the perioperative period to attenuate the surgical stress response and to alleviate postoperative pain have also been demonstrated to protect against myocardial ischemia and reperfusion injury through activation of opioid receptor subtypes, including δ-, κ-, and μ-receptors.

In the current investigation, patients were randomly assigned to receive either sevoflurane or propofol for the maintenance of anesthesia, and the intraoperative management of patients was left to the discretion of the attending anesthesiologist. This approach has both advantages and disadvantages. An advantage is that, had volatile anesthetics been shown to decrease myocardial ischemia compared with propofol, this result would have been more broadly generalizable to other institutions with different practice patterns and usage of anesthetic adjuvants, such as opioids, vasoactive drugs, and benzodiazepines that contribute to postoperative neurocognitive dysfunction in elderly patients. The latter is relevant because postoperative delirium was a tertiary end point of the study. Unfortunately, in the absence of any detail regarding the intraoperative management of patients or hemodynamics, a negative finding is less easily interpreted. For example, experimental studies indicate that the cardioprotective effects of volatile anesthetics are dose dependent. However, direct comparisons of anesthetic doses may be practically difficult to achieve. In the case of volatile anesthetics, dose is exhaled gas concentration expressed in relation to the motor response to surgical stimulation (minimum alveolar concentration), whereas propofol dose is gravimetric (in milligrams per kilogram). This limitation might have been partially overcome by using bispectral analysis to guide...
administration of anesthetics to achieve similar levels of anesthetic depth, although the effects of various anesthetics on the central nervous system versus the cardiovascular system may not be equipotent or comparable. The intraoperative and postoperative use of drugs such as opioids, β-blockers, and α-2 agonists could also have influenced the results. Opioids activate similar signaling pathways as volatile anesthetics and enhance the preconditioning effect of isoflurane. Thus, the use of opioids in patients receiving either propofol or sevoflurane, although not reported by Buse et al., could have confounded the results.

The influence of systemic hemodynamics on perioperative myocardial ischemia has been demonstrated previously in patients undergoing vascular and cardiac surgery. Raby et al. reported a decreased incidence of myocardial ischemia in patients undergoing vascular surgery who were randomized to receive esmolol versus placebo to control heart rate below an ischemic threshold determined preoperatively with continuous electrocardiography. In a seminal investigation, Slogoff and Keats evaluated the relationship between perioperative myocardial ischemia and postoperative myocardial infarction in patients undergoing coronary artery bypass graft surgery. Electrocardiographic ischemia was detected in 36.9% of patients, and ischemia was significantly more likely to occur in patients during hemodynamic abnormalities, predominantly tachycardia, occurring during tracheal intubation and surgical stimulation. Subsequently, these investigators showed that the incidence of perioperative myocardial ischemia and major adverse cardiovascular events were similar in 1012 cardiac surgical patients randomized to receive either a volatile anesthetic or high-dose opioids as the primary anesthetic technique. Intraoperative management was standardized, and hemodynamics were tightly controlled in this trial. Interestingly, Slogoff and Keats also evaluated the role of the anesthesiologist as a determinant of perioperative ischemia and postoperative myocardial infarction in their earlier investigation. One of the 9 participating anesthesiologists had significantly higher rates of intraoperative tachycardia and myocardial ischemia, possibly attributable to the method of inducing anesthesia and controlling hemodynamics during intubation.

The evolution of opinion in favor or against the use of volatile anesthetics for cardioprotection is reminiscent of the case of β-blockers for perioperative risk reduction. β-Blockers may be very useful, but if given in doses sufficient to cause adverse postoperative hemodynamic effects or during surgical anemia, their beneficial effects may not be realized. Over the last 10 to 20 years, the medical management of patients with cardiac disease undergoing surgery has changed considerably. Asymptomatic myocardial ischemia is recognized as a critical problem that is observed in approximately 50% of ambulatory patients with stable coronary artery disease. It is a significant predictor of mortality, and appropriate medical therapy to reduce silent ischemia is an important goal. It has been suggested that the specific anti-ischemic regimen that is used (that may include a variety of drugs, eg, β-blockers, statins, aspirin, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers) may be of less importance than ensuring that heart rate is adequately sup-pressed. The degree of silent ischemia (frequency and severity) has also been suggested to be more important in predicting cardiac events than the mere presence or absence of ischemia. An important limitation of the study by Buse et al. is that total ischemic burden was not quantified and may have differed between the groups.

Seventy percent of patients in the current trial were on chronic aspirin and β-blocker therapy; ≥60% were taking statins and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Thus, it is unclear whether the negative findings of the investigation indicate a lack of volatile anesthetic cardioprotection, per se, or the influence of additional factors that also modulate the incidence of perioperative myocardial ischemia. Finally, volatile anesthetics are routinely administered for the maintenance of general anesthesia and, considering nationwide drug shortages, including propofol, the choice of anesthetic agent may be immaterial. So what is the best recipe for perioperative cardioprotection? No one ingredient may tip the balance, but the skilful approach of the anesthesiologist makes the best cake.

Disclosures

None.

References


Key Words: Editorials ■ anesthesia ■ cardiovascular diseases ■ ischemia ■ pharmacology ■ surgery
A Recipe for Perioperative Cardioprotection: What Matters Most? The Ingredients or the Chef?
Judy R. Kersten