Volatile anesthetics in cardiac surgery: Renoprotective, cardioprotective, neither, or both?

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Preclinical and clinical studies have suggested that volatile anesthetics may provide end-organ protection during surgery by attenuating ischemia-reperfusion injury through ischemic preconditioning.¹ The cardioprotective effects of volatile anesthetics during heart surgery were suggested most convincingly by a meta-analysis of randomized controlled trials (RCTs) published by Landoni and colleagues² in 2007, which demonstrated reductions in cardiac troponin I release, myocardial infarction, need for inotropic support, intensive care unit and total hospital length of stay, and all-cause mortality with use of newer volatile anesthetics (desflurane and sevoflurane) in comparison with total intravenous anesthesia. In 2012, an international consensus conference further identified the use of volatile anesthetic during cardiac surgery as 1 of only 14 nonsurgical interventions supported by randomized evidence that may reduce perioperative mortality.³ However, data supporting the renoprotective effects of volatile anesthetics during cardiac surgery has been mixed. In the current issue of the *Journal of Thoracic and Cardiovascular Surgery*, Cai and colleagues⁴ attempted to resolve this controversy by performing a laudable meta-analysis of RCTs to assess the impact of volatile anesthetics on the risk of acute kidney injury (AKI) after heart surgery. The primary study finding was that the use of volatile anesthetic was associated with a reduced risk of postoperative AKI relative to total intravenous anesthesia (relative risk, 0.65). Although mechanistically plausible, several considerations should influence the interpretation of these results.

The authors identified a total of 10 RCTs that met the study inclusion criteria. Only 7 of these trials reported postoperative AKI and 4 different AKI definitions were used. Notably, standardized definitions for postoperative AKI, such as the Society of Thoracic Surgeons or Acute Dialysis Quality Initiative Workgroup RIFLE (Risk,

Injury, Failure, Loss, End-stage renal disease) criteria⁵ were not used in any of the RCTs. Amongst these 7 trials, the protocols for anesthesia use differed widely. In the volatile anesthetic arms, the volatile agents were initiated at various time points and continued for different durations, ranging from throughout the procedure to only 10 minutes during cardiopulmonary bypass, suggesting intravenous anesthetics were likely used for significant portions of the procedures in some instances. In the total intravenous anesthesia arms, agents with vastly different pharmacologic profiles were used, including propofol alone, propofol and midazolam, and sufentanil and midazolam. The procedures performed in the different trials included coronary artery bypass grafting (CABG), valve operations, and even off-pump CABG, leading to substantial variation in the circulatory and ischemic stresses experienced by the patients in the study. The significant heterogeneity in clinical protocols and definitions of outcomes between the trials clouds the veracity of the cumulative meta-analysis result.

In addition to the small number of trials with heterogeneous protocols, the magnitude of the treatment effect seemed small and perhaps clinically insignificant. The primary study finding of reduced AKI narrowly reached statistical significance (95% confidence interval, 0.43-0.97; $P = .04$). Furthermore, the meta-analysis found no difference in absolute postoperative creatinine or cystatin C levels at any time point. The authors next explored changes in postoperative creatinine levels over baseline in 6 studies where baseline and serial postoperative creatinine levels were reported. Here, the results showed that postoperative creatinine levels increased 0.04 mg/dL less over baseline on postoperative day 1 ($P = .002$) and 0.07 mg/dL less over baseline on postoperative day 2 ($P = .05$) with use of volatile anesthetics. Although these findings were statistically significant, the clinical relevance of creatinine reductions of 0.04 to 0.07 mg/dL remains questionable. Consistent with the small magnitude of the treatment effect suggested here, use of volatile anesthetic was not associated with a reduced risk of renal replacement therapy in the 2 studies that reported this outcome.

Despite these limitations, the finding of a small but significant reduction in postoperative AKI with the use of volatile anesthetics during cardiac surgery is plausible and may in fact be entirely accurate. Volatile anesthetics may impart direct renoprotective benefits through similar ischemic preconditioning mechanisms that are believed to protect the

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heart.⁶ Alternatively, the kidneys may simply be innocent bystanders that benefit from improved cardiac performance (improved cardiac output and hemodynamic stability, reduced hypotension, and inotrope use), as a result of the cardioprotective effects of volatile anesthetics. The latter explanation seems more likely given that pronounced improvements in intensive care unit (ICU) and hospital length of stay, and potentially even mortality,² are unlikely to result from minute improvements in kidney function alone, suggesting a larger force is at play. Alternatively, reduced AKI and reduced ICU and hospital length of stay may simply be sequelae of reduced hypotension and quicker emergence from anesthesia and extubation by avoidance of prolonged exposure to propofol, and not a result of ischemic end-organ protection.

Although several uncertainties remain, the present study and others are likely to support the continued trend toward increased use of volatile anesthetics during cardiac surgery. However, additional randomized trials are needed to

confirm the beneficial effects of these agents and elucidate the optimal patient population and protocol for their use.

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