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Sevoflurane- Compared with Propofol-based Anesthesia Reduces the Need for Inotropic Support in Patients Undergoing Abdominal Aortic Aneurysm Repair: Evidence of Cardioprotection by Volatile Anesthetics in Noncardiac Surgery

To the Editor:

We read with interest the study by Lindholm *et al.*[1] comparing cardioprotection by sevoflurane- and propofol-based anesthesia in patients undergoing elective abdominal aortic surgery. The authors chose cardiac troponin T (cTnT) release determined at one single postoperative time point as the primary endpoint of cardioprotection. No difference between the groups was found, and the authors concluded that *"potential cardioprotective effects of volatile anesthetics found in cardiac surgery are less obvious in major vascular surgery."*[1]

We do not agree with this interpretation of the study results. Neither do we think that this study, as designed *a priori and ultimately conducted*, properly addresses the stated hypothesis. First, the cardioprotective effects of sevoflurane are not *"less obvious in major vascular surgery,"* but indeed *very similar* to what was reported for volatile anesthetics in previous studies with patients undergoing cardiac surgery in the on-pump[2,3] or off-pump mode.[4,5] In fact, Lindholm *et al.*[1] report a significantly reduced need for inotropic support in the sevoflurane group ($P = 0.003$), implying improved cardiac function and reflecting a clear advantage of the sevoflurane-based anesthesia. Unfortunately, this important finding is only briefly mentioned in the Results section and completely ignored in the Discussion. No details on the doses of dopamine and noradrenaline or other potentially administered inotropics such as ephedrine and/or phenylephrine are provided. From the currently available eight randomized trials evaluating volatile anesthetic-induced cardioprotection in patients undergoing off-pump coronary artery bypass graft surgery, a type of surgery which is in many aspects comparable with abdominal aortic aneurysm repair, only three of eight (37%) find reductions in cardiac troponin release, whereas four of eight (50%) find improved cardiac function or reductions in inflammatory markers. Although infarct size and the release of cardiac enzymes are the "definitive standard" of cardioprotection, they are by far not the only clinically relevant outcome measures. Cardioprotection in patient care has already reached a high standard, and any additional protection may be unable to further reduce perioperative release of myocardial necrosis markers, specifically so if the majority of patients are already treated with statins, aspirin, β-blockers, and thoracic epidural anesthetics. In support of this, the use of a volatile anesthetic in cardiac surgical patients potentially reduces long-term cardiovascular complications and mortality, as shown by Garcia *et al.*,[6] De Hert *et al.*,[7] and others,[8,9] despite the clear absence of a reduction in perioperative cardiac troponin release. This notion is compatible with the strong anti-inflammatory and potentially plaque-stabilizing actions of volatile anesthetics[5] during the critical perioperative period. We also think that serial postoperative determinations of cTnT should have been obtained in the study by Lindholm *et al.*[1] to reliably map postoperative myocardial damage, and if reporting cTnT values of a single postoperative time point, a histogram of the results displaying ranges of cTnT levels and numbers of patients would provide much more information.

Second, we think that the design of the study by Lindholm *et al.*[1] does not allow to directly answer the hypothesis whether a sevoflurane-based anesthesia as compared with a propofol-based anesthesia is more cardioprotective, because in their sevoflurane group, fentanyl was used as opioid whereas in the propofol group remifentanil was used. Current clinical studies with remifentanil suggest that its cardioprotection may render the protective effects of volatile anesthetics redundant.[10–12] Studying the interference in cardioprotection by volatile anesthetics, opioids and propofol in a working rat heart model, we recently demonstrated that remifentanil maintains its protection against ischemia–reperfusion injury in combination with propofol, but does not further enhance protection by sevoflurane.[13] Furthermore, in the study by Lindholm *et al.*,[1] patients randomized to propofol-based anesthesia were clearly more aggressively treated with aspirin and β-blockers, making the study groups unbalanced and shifting cardioprotection in favor of the propofol group. Also,

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we have recently shown that the volatile anesthetic isoflurane masks cardioprotection by remote ischemic preconditioning in patients undergoing coronary artery bypass surgery.[14] Hence, potential cardioprotection by remote ischemic conditioning through aortic cross-clamping, if materializing at all in anesthetized as opposed to awake patients,[15] may be less pronounced in the sevoflurane compared with the propofol group.

Finally, it is unfortunate that the cause of death was not available due to restrictions on the access to the registry. In such a case, a prospectively defined cardiovascular evaluation of fatal and nonfatal cardiovascular adverse events including changes in cardiovascular medications during the long-term follow-up is warranted. Unfortunately, the authors also failed to perform logistic regression analyses to identify variables independently associated with cTnT or long-term mortality. Important candidate variables would include group assignment, inotropic support, use of β-blockers, statins, aspirin, and heart rate. Multivariate Cox proportional hazards models should have been used to determine associations of cTnT categories with mortality after serially adjusting for traditional risk factors.

In conclusion, lack of detailed analyses seems to be a major problem of the currently available data evaluating cardioprotection by volatile anesthetics in noncardiac surgery.[16] In contrast to the authors themselves, we think that the study by Lindholm *et al.*[1] indeed suggests superior cardioprotection by sevoflurane compared with propofol in patients undergoing noncardiac surgery for abdominal aortic aneurysm repair, despite the multiple limitations and confounding issues as detailed above.

Competing Interests

The authors declare no competing interests.

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