Cardiac anesthesia is associated with ischemia-reperfusion injury. Trying to limit the extent and mitigate the consequences of ischemia could potentially improve outcome after cardiac surgery. In the last 10 to 15 years, volatile agents have been shown to improve outcome in cardiac surgery. Despite these data, volatile anesthesia is not the most widely used technique for cardiac anesthesia. In the previous issue of *Critical Care*, Steurer and colleagues [1] presented interesting data on sevoflurane administration following cardiac surgery. These data have to be placed in the context of already-accumulated evidence and potential clinical applications.

Anesthetic gases are fascinating drugs: First-generation anesthetic gases, especially halothane, had significant cardiac side effects, increasing the risk of malignant arrhythmia and sensitizing the heart to catecholamines. Further generations, especially sevoflurane, have been shown to have interesting neuro- and cardioprotective properties. In the last 10 to 15 years, a wealth of data has shown that peri-operative administration of halogenated agents is associated with myocardial protection and better outcome.

Darwin proposed that species adapt to environment, the better-adapted breed having the better chances of survival. Interestingly, at the tissue, cell, mitochondrion, and possibly the gene level, there is a dynamic adaptation to the environment. This led to the concept of preconditioning, a mechanism in which brief sublethal periods of ischemia will provide protection from a subsequent lethal ischemia and mitigate the effect of ischemia-reperfusion [2]. As stated by Friedrich Nietzsche, ‘What does not destroy me, makes me stronger’. The organism or the tissue will acquire some ‘injury-resistant’ phenotype for a certain period of time [3]. Ischemic pre-conditioning is an interesting and powerful concept, but its clinical applicability is limited by the already-jeopardized myocardium.

All hypnotics decrease myocardial consumption and may favor the myocardial oxygen supply/demand balance. On top of these macrohemodynamic effects, halogenated agents have intrinsic cardio- and neuroprotective effects that are similar to those of ischemic pre-conditioning. At a basic science level, the myocardial protection effects of sevoflurane involve apoptotic mRNA inhibition, neuro-modulation, cytokine/inflammation modulation, redox-sensitive pathways, endothelial preservation, ion channels, notch signaling pathways, and probably other mechanisms to be discovered. This translates clinically as a decrease in post-cardiac surgery troponin levels, lower inotropes requirements, and better cardiac output. Pre-conditioning is well established, and volatile agents are now recommended as the agent of choice by the American Heart Association for high-risk patients [4].

However, pre-conditioning is difficult to apply once the injury has already been established. Interestingly, brief periods of ischemia at the onset of the reperfusion period are associated with cardioprotection, leading to a myocardial infarction size decrease similar to [5] or slightly inferior to that of ischemic pre-conditioning [6]. Isoflurane has been shown to improve remodeling after coronary artery occlusion in rats [7]. In a similarly designed animal model of circulatory arrest published last year in this journal, sevoflurane administered immediately after the return of spontaneous circulation decreased myocardial...
Table 1. Some research questions regarding sevoflurane post-conditioning

| Question                                                                                           |
|----------------------------------------------------------------------------------------------------|
| Is the post-conditioning effect related to the "dose" of sevoflurane?                              |
| Is there a minimum duration or minimum alveolar concentration to obtain post-conditioning?        |
| Is there a dose response curve on sevoflurane post-conditioning?                                   |
| Do all volatile anesthetic agents (isoflurane or desflurane) provide the same post-conditioning?  |
| Does the lower release in cardiac damage markers shown by Steurer et al. [1] translate into outcome |
| differences? Lower myocardial infarction rates? Lower inotropic support?                          |
| Better cardiac output? Shorter intensive care unit/hospital stays? Lower mortality? Lower resource  |
| utilization?                                                                                       |
| How long is the therapeutic window after reperfusion to exhibit a post-conditioning organ protection?|
| That is, how long after cardiopulmonary bypass or injury does sevoflurane have to be started to induce post-conditioning? |
| Is there an additional cardioprotective effect when sevoflurane is used intraoperatively (pre-conditioning)? |
| Is there a protective effect on other organs such as the brain or the kidney?                       |
| Animal data suggest that post-conditioning is better in males [16] and inhibited by hyperglycemia [17]: Is post-conditioning beneficial only in males or in the context of tight glucose control (or both)? |
| Sevoflurane administration is associated with plasma fluoride levels above upper limit. How long can we use sevoflurane for sedation/post-conditioning in terms of fluoride toxicity? |

Sevoflurane and isoflurane are very flexible generic anesthetic drugs administered daily by numerous anesthetists around the world. The demonstration of cardio- or neuroprotective effects (or both) when applied after the ischemia will make them interesting in myocardial ischemia, cardiogenic shock, or even traumatic brain injuries. Sevoflurane administration in the ICU has been done previously [12,13]. It has been shown to be associated with fast awakening/weaning times after the drug is stopped [12]. The anesthesia-conserving device has made the delivery simple and adaptable on 'regular' ICU-type ventilators. However, technical aspects such as gas analyzers, concentration measurement, and exhausted gas scavenging (most ICU-type ventilators release the exhaust gases into the environment) need to be taken into account. Educational aspects must include nurse training, dosage, availability of dantrolene, and training for the unlikely event of a malignant hyperthermia reaction. In addition, data show plasma fluoride concentration (39 ± 25 μmol/L) close to safety limits (50 μmol/L) at 24 and 48 hours after 9 hours of sevoflurane [14]. Sevoflurane administration beyond 12 to 24 hours needs to be assessed in terms of fluoride plasma concentration and nephrotoxicity. Environmental effects of widespread anesthetic gas use need to be taken into account [15]. Most cardiac surgery patients require a maximum of a few hours of mechanical ventilation (if any). In these circumstances, sevoflurane sedation in the cardiac ICU may be a very flexible option with an additional myocardial protection benefit.

Conclusions

Sevoflurane and possibly other volatile anesthetic agents show promising post-conditioning properties after cardiac surgery. This opens a new field of investigations and potential therapies aiming at mitigating secondary myocardial injury after the primary injury is done. More data are necessary to assess the magnitude conferred by this protection, its clinical relevance, the window of opportunity, and the collateral protection on other organs. Very promising answers, and more questions, are to come.

Abbreviation

ICU, intensive care unit.

Competing interests

The author declares that he has no competing interests.

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References

1. Steurer MP, Steurer MA, Baulig W, Piegeler T, Schläfper M, Spahn DR, Fahl V, Dreessen P, Theusinge OM, Smidt ER, Schwartz D, Neff TA, Beck-Schimmer B: Late pharmacological conditioning with volatile anaesthetics after cardiac surgery. Crit Care 2012, 16 R191.
2. Murry CE, Jennings RB, Reimer KA: Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. Circulation 1986, 74:124-1136.
3. Gidday JM: Cerebral preconditioning and ischaemic tolerance. Nat Rev Neurosci 2006, 7:437-448.
4. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof EL, Fleischmann KE, Freeman WK, Froehlich JB, Kasper EK, Kersten JR, Riegel B, Robb JF, Smith SC Jr., Jacobs AK, Adams CD, Anderson JL, Antman EM, Beller CE, Creager MA, Ettinger SM, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Nishimura R, Omato JP, Page RL, Riegel B, Tarkington LG, Yancy CW: ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. J Am Coll Cardiol 2007, 50:1707-1732.

5. Zhao ZQ, Corvera JS, Halkos ME, Kerendi F, Wang NP, Guyton RA, Vinten-Johansen J: Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. Am J Physiol Heart Circ Physiol 2003, 285:H579-588.

6. Kin H, Zhao ZQ, Sun HY, Wang NP, Corvera JS, Halkos ME, Kerendi F, Guyton RA, Vinten-Johansen J: Postconditioning attenuates myocardial ischemia-reperfusion injury by inhibiting events in the early minutes of reperfusion. Cardiovasc Res 2004, 62:74-85.

7. Feng J, Fischer G, Lucchinetti E, Zhu M, Bestmann L, Jegger D, Arras M, Pasch T, Periard JC, Schaub MC, Zaugg M: Infarct-remodeled myocardium is receptive to protection by isoflurane postconditioning: role of protein kinase B/Akt signaling. Anesthesiology 2006, 104:1004-1014.

8. Meybohm P, Gruenewald M, Albrecht M, Müller C, Zitta K, Foessel N, Maracke M, Tacke S, Schrezenmeier J, Scholz J, Bein B: Pharmacological postconditioning with sevoflurane after cardiopulmonary resuscitation reduces myocardial dysfunction. Crit Care 2011, 15:R241.

9. Feng J, Lucchinetti E, Ahuja P, Pasch T, Periard JC, Zaugg M: Isoflurane postconditioning prevents opening of the mitochondrial permeability transition pore through inhibition of glycogen synthase kinase 3beta. Anesthesiology 2005, 103:987-995.

10. Yu LN, Yu J, Zhang FJ, Yang MJ, Ding TT, Wang JK, He W, Fang T, Chen G, Yan M: Sevoflurane postconditioning reduces myocardial reperfusion injury in rat isolated hearts via activation of PI3K/Akt signaling and modulation of Bcl-2 family proteins. J Zhejiang Univ Sci B 2010, 11:661-672.

11. Lemoine S, Beaufuchet G, Zhu L, Renard E, Lepage G, Massetti M, Khayat A, Galera P, Gerard JL, Hainoz JL: Signaling pathways involved in desflurane-induced postconditioning in human atrial myocardium in vitro. Anesthesiology 2008, 109:1036-1044.

12. Mesnil M, Capdevila X, Bringuer S, Trine PQ, Falquet Y, Charbit J, Roustan JP, Chanches G, Jaber S: Long-term sedation in intensive care unit: a randomized comparison between inhaled sevoflurane and intravenous propofol or midazolam. Intensive Care Med 2011, 37:933-941.

13. Pratt PF Jr., Wang C, Welrauch D, Bienengraeber MW, Kersten JR, Pagel PS, Wartlir DC: Cardioprotection by volatile anesthetics: new applications for old drugs? Curr Opin Anaesthesiol 2006, 19:397-403.

14. Rohm KD, Mengistu A, Boldt J, Mayer J, Beck G, Piper SN: Renal integrity in sevoflurane sedation in the intensive care unit with the anesthetic-conserving device: a comparison with intravenous propofol sedation. Anesth Analg 2009, 108:1849-1854.

15. Sulbaek Andersen MP, Sander SP, Nielsen OJ, Wagner DS, Sanford TJ Jr, Wallington TJ: Inhalation anaesthetics and climate change. Br J Anaesth 2010, 105:760-766.

16. Zheng Z, Yang M, Zhang F, Yu J, Wang J, Ma L, Zhong Y, Qian L, Chen G, Yu L, Yan M: Gender-related difference of sevoflurane postconditioning in isolated rat hearts: focus on phosphatidylinositol-3 kinase/Akt signaling. J Surg Res 2011, 170:e3-9.

17. Inamura Y, Miyamae M, Sugioka S, Domae N, Kotani J: Sevoflurane postconditioning prevents activation of caspase 3 and 9 through antiapoptotic signaling after myocardial ischemia-reperfusion. J Anesth 2010, 24:215-224.

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