Volatile anesthetic preconditioning modulates oxidative stress and nitric oxide in patients undergoing coronary artery bypass grafting

Sathish Kumar Dharmalingam, G Jayakumar Amirtharaj, Anup Ramachandran, Mary Korula

Department of Anaesthesiology, The Wellcome Trust Research Laboratory, Division of Gastrointestinal Sciences, Christian Medical College, Ida Scudder Road, Vellore, Tamil Nadu, India, Department of Pharmacology, Toxicology and Therapeutics, University of Kansas Medical Center, Kansas City, KS 66160, USA

Institute at which the study was conducted: Christian Medical College and Hospital, Ida Scudder Road, Vellore, India.

ABSTRACT

Background: Myocardial preconditioning using volatile anesthetics such as isoflurane and sevoflurane have beneficial effects in decreasing morbidity in cardiac surgical patients. Studies in animal models have indicated that reactive oxygen and nitrogen species probably play a role in mediating these effects. However, data from human studies are scarce and the differential effect of sevoflurane vs. isoflurane on reactive oxygen species (ROS) and reactive nitrogen species (RNS) has not been studied extensively.

Materials and Methods: Randomized clinical control trial comparing preconditioning effects of volatile agents isoflurane and sevoflurane when administered during coronary artery bypass surgeries on cardiopulmonary bypass (CPB). Serum samples were collected at 3 time points before induction, after cross clamp release and one hour after separation from CPB. Levels of oxidative stress markers and nitric oxide were analyzed in these samples.

Results: Hemodynamic indices, cardio-pulmonary bypass duration, and ICU stay were similar between the groups. CKMB values 12 hours post-op were decreased in majority of patients in the sevoflurane group compared to isoflurane. Serum malondialdehyde and nitrate levels were lower with sevoflurane ($P < 0.05$) when compared to the isoflurane group, but no significant differences in protein carbonyl content or protein thiol content were evident between the 2 groups. Sevoflurane also prevented the decrease in total thiols during later stages of surgery.

Conclusions: Volatile anesthetics, isoflurane and sevoflurane modulate oxidative and nitrosative stress during CABG. Between the two pre-conditioning agents, isoflurane seems to provide better protection during the pre-bypass period, while sevoflurane provides protection during both pre- as well as post-bypass period.

Keywords: Cardiopulmonary bypass, isoflurane, nitric oxide, oxidative stress, sevoflurane

INTRODUCTION

Preservation of myocardial contractility is essential in any cardiac surgical procedures for better outcome. However, higher mortality rates are observed in patients with poor preoperative cardiac function, complicated coronary artery disease requiring multiple interventions, incomplete myocardial revascularization and prolonged surgical duration with increased cross clamp time. In order to
Among the interventions for myocardial preservation, myocardial ischemic preconditioning has received significant interest. Myocardial preconditioning can be achieved by various methods, including volatile agents such as halothane, enflurane, isoflurane, and sevoflurane. Among these, isoflurane and sevoflurane have been shown to be better preconditioning agents in some studies, though the mechanisms behind their beneficial effect are not well understood. A meta-analysis of 27 randomized trials comparing volatile with non-volatile anesthesia in CABG surgery revealed that the patients received volatile anesthetics had 20% higher cardiac indices, significantly lower troponin I serum concentrations, lesser requirement for inotropic support and reduced duration of mechanical ventilation when compared with those received intravenous anesthetics.

Reactive oxygen species (ROS) are central to cardiac ischemic and reperfusion injury but paradoxically have also been implicated for the beneficial effects of volatile anesthetics used in pre-conditioning. In vitro experiments and animal studies have indicated that reactive oxygen species (ROS) and nitric oxide play a role in mediating pre-conditioning with agents like isoflurane and sevoflurane. Experiments with guinea pig hearts have demonstrated that anesthetic preconditioning is triggered by reactive oxygen/nitrogen species. Reactive oxygen species have been shown to mediate sevoflurane and desflurane-induced preconditioning in isolated human right atria in vitro. Experiments in rat right ventricular trabeculae have shown that sevoflurane-induced cardio protection depends on PKC-alpha activation via production of reactive oxygen species and it can also lead to decreased superoxide production during ischemia and reperfusion in isolated hearts.

Nitric oxide is also now emerging as an important signaling molecule, and in an animal model of off-pump CABG, it has been shown that circulating levels of nitric oxide decrease by 10 minutes after reperfusion, but subsequently increases significantly by 24 hours after reperfusion. The beneficial effect of pre-conditioning by volatile anesthetics has been shown to reduce nitric oxide levels. Anesthetic agents have shown to modulate ROS and nitric oxide synthase levels while enhancing ethanol-induced cardiac preconditioning in animal models. However, studies in humans are scarce and this study examines the effect of two volatile anesthetics, namely isoflurane and sevoflurane on ROS and NO in patients undergoing CABG. We hypothesized that clinical benefit from these anesthetics would be dependent on the degree of their effect on ROS and NO metabolism. This concept was tested by examining the effect of these two volatile anesthetics on systemic oxidative/nitrosative stress in patients undergoing CABG on CPB.

### MATERIALS AND METHODS

**Materials:** 1,1,3,3 tetramethoxy propane, 2-thiobarbituric acid (TBA), 2,4 dinitro phenyl hydrazine (DNPH), Tris (hydroxymethyl) aminomethane (Tris), ethylene diamine tetra acetic acid (EDTA), 5',5' dithio-bis-(2-nitro benzoic acid) (DTNB), sulfanilamide and N-naphthylethylenediamine dihydrochloride were obtained from Sigma Chemical Co., St Louis, MO, U.S.A. All other chemicals and solvents used were of analytical grade.

**Patients:** Eighteen patients between 35 and 65 years of age scheduled for coronary artery bypass grafting on CPB were randomly allocated to receive either Isoflurane (group 1) or Sevoflurane (group 2). Patients with previous cardiac operations, combined valvular surgeries and unstable patients requiring ionotropes or mechanical ventilator support in the preoperative period were excluded from the study. Patients were premedicated with lorazepam, induced with midazolam (2-3 mg), fentanyl (3-5 mcg/kg), vecuronium, air, oxygen, and isoflurane (group 1) or sevoflurane (group 2) and maintained with the same anesthetic agent. Apart from routine monitoring hemodynamic indices such as cardiac output (CO), cardiac index (CI), and systemic vascular resistance (SVR) were measured intermittently in all patients during the pre-bypass period and after coming off CPB when the patient was stable, using pulmonary artery catheter inserted through right internal jugular vein. An average of three values were taken at both pre and post bypass period. During CPB, isoflurane or sevoflurane was administered via a special vaporizer attached to the pump by maintaining the bi spectral index (BIS) value around 40-60. After coming off pump, anesthesia was maintained with morphine (0.1 to 0.2 mg/kg), vecuronium, isoflurane or sevoflurane, air, and oxygen. Samples for analysis of oxidative/nitrosative stress were collected at 3 time points: (a) before induction (b) 60 minutes after aortic cross clamp release and (c) 60 minutes after separation of pump. The study was approved by the Institutional Research Committee and samples were collected after informed consent. Routine CPB with cold St Thomas cardioplegia was used in all patients. Anticoagulation was established by using heparin 3 to 4 mg/kg and an ACT...
was maintained >450 secs throughout the bypass period. Protamine was used to reverse the heparin at a ratio of 1:1 to 1:1.2 (ACT <140 secs) at the end of CPB.

**Measurement of malondialdehyde & protein carbonyl content:** Malondialdehyde content was measured as described by Ohkawa H et al.[13] Protein carbonyl content in the serum was measured using dinitro phenyl hydrazine (DNPH) and HCl.[14]

**Estimation of thiol groups:** Thiol content of the sample was measured by the methods described by Habeeb using Ellman’s reagent.[15]

**Measurement of nitrate:** For analysis, nitrate in the samples was first reduced to nitrite, which is then measured by the Griess reaction. Reduction of nitrate to nitrite was carried out using a copper-cadmium alloy as described by Sastry KV et al.[16]

**Statistical Analysis:** Results are expressed as means ± SD and ± S.E.M. Student t test was performed for statistical analysis. A P value of less than 0.05 was taken to indicate statistical significance.

**RESULTS**

Patients in both groups recruited for the study showed no significant difference in age, weight, height, gender, or pre-morbidity status [Table 1a and b]. Hemodynamic data including cardiac indices such as cardiac output, cardiac index, and systemic vascular resistance also showed no statistical difference between groups [Table 2a]. No differences between groups were seen in cardio-pulmonary bypass duration or duration of ICU stay [Table 2b]. However, CK-MB values at 12 hours post-op showed a decrease in 7 of the 9 patients in the sevoflurane group, while only 4 out of the 9 in the isoflurane group showed a decrease [Figure 1].

For evaluation of oxidative and nitrosative stress, 3 blood samples were taken at different time points; sample A at pre induction, sample B one hour after cross clamp release and sample C one hour after coming off bypass. Parameters of oxidative and nitrosative stress such as protein thiols, total thiols, protein carbonyls, malondialdehyde, and nitrates were measured in each sample.

Malondialdehyde is one of the main products of lipid peroxidation and an increase of its level in serum indicates oxidative stress. Figure 2a shows the levels of malondialdehyde in serum from patients at different time points during CABG. As seen in the Figure 2a presence of sevoflurane results in a decrease in malondialdehyde levels suggestive of protection against oxidative stress. This was not evident in the isoflurane group, which did not change. However, during the reperfusion phase after bypass, presence of isoflurane prevented any increase in malondialdehyde, suggesting protection against lipid peroxidation. The effect of sevoflurane during this phase is more dramatic, since the decrease in malondialdehyde levels initiated in the ischemic phase is sustained. This indicates that presence of sevoflurane provides better protection against lipid peroxidation both during pre as well as post bypass period when compared to isoflurane. Again it should be noted that presence of isoflurane prevented the expected increase in malondialdehyde during reperfusion, an effect which could not be demonstrated in this study due to absence of a control group (who would not have received any inhalation agent on pump) due to ethical reasons.

Proteins are important targets of oxidative stress, and protein carbonyl content is a marker of protein oxidation. Oxidative stress in serum would thus result in an increase in protein carbonyl content. Figure 2b shows the levels of serum protein carbonyls in both isoflurane and sevoflurane treated groups. As can be seen, during the ischemic pre bypass period patients in both groups show a decrease in protein carbonyl content. In the post bypass period during reperfusion, levels do not change, though the sevoflurane groups show a very slight increase, which did not attain significance. Protein carbonyl content is similar between the groups at the later time points B and C. This data indicates that presence of either anesthetic in the CPB

---

**Table 1a: Demographic Data**

| Parameter          | Group – I (n=9) | Group – II (n=9) | P  |
|--------------------|-----------------|-----------------|----|
| Age (years)        | 55.7±9.42       | 52.6±7.99       | 0.461 |
| Height (cms)       | 166.78±6.8      | 163.11±7.47     | 0.293 |
| Weight (kgs)       | 65.89±12.150    | 65.89±12.150    | 0.108 |

**Table 1b: Pre-operative morbidity**

| Morbidity factors                | Group 1 (n=9) | Group 2 (n=9) | P  |
|----------------------------------|---------------|---------------|----|
| NYHA CLASS                       |               |               |    |
| I                                | 0             | 0             |    |
| II                               | 6             | 7             | 0.6 |
| III                              | 3             | 2             |    |
| IV                               | 0             | 0             |    |
| Hypertension                     |               |               |    |
| LV dysfunction (angiogram)       |               |               |    |
| I                                | 5             | 5             | 1.0 |
| II                               | 2             | 4             | 0.62 |
| III                              | 2             | 2             |    |
| IV                               | 7             | 6             | 0.58 |
| Diabetes mellitus                |               |               |    |
| LV- Left ventricle, MR- Mitral Regurgitation |

---

Dharmalingam, et al.: Volatile anesthetics and oxidative stress in CABG
pump during CABG prevents protein oxidation and has a beneficial effect.

Thiols are anti-oxidant and it is necessary for normal cellular function. Thiol groups on proteins also have critical roles in protein function and are also susceptible to damage by ROS. Oxidative stress would result in a decrease in total thiol content, which may be accompanied by decreases in protein thiols if thiol groups on proteins are damaged. As seen in Figure 3a, patients in the isoflurane group had an increase in total thiols after initiation of ischemia by cross clamping. This could be due to a decrease in constitutive levels of free radicals because of a lack of oxygen, resulting in sparing of thiol anti-oxidants. However, after subsequent reperfusion (point C) thiol levels show a sharp decrease, which is expected since reperfusion would result in a significant increase in ROS production. It is interesting to note that the response with sevoflurane is different from that for isoflurane. Serum total thiol shows a slight decrease during ischemia and then does not change during reperfusion, in fact showing a slight increase. This indicates that presence of sevoflurane is able to spare thiols during reperfusion and has a beneficial effect during later stages. It should be noted however, that if neither isoflurane nor sevoflurane were used in pump, the changes in thiols would probably have been more dramatic. Examination of protein thiols [Figure 3b] show that serum levels of protein thiols are decreased in both pre and post CABG period when compared to the initial baseline level. This indicates that oxidative stress during CABG did affect thiol groups on proteins. The levels are not different in presence of either isoflurane or sevoflurane at the later time points, namely, one hour after cross clamping and one hour after coming off bypass.

### Table 2a: Hemodynamic indices with Isoflurane and Sevoflurane

|                      | BASAL      | PRE CPB   | POST CPB  | P     |
|----------------------|------------|-----------|-----------|-------|
| **MAP (mmhg)**       |            |           |           |       |
| Isoflurane           | 87.77±7.57 | 74.11±8.90| 75.77±8.12| 0.673 |
| Sevoflurane          | 90.33±7.85 | 74.77±8.01| 73.33±8.07| 0.920 |
| **CVP (mmhg)**       |            |           |           |       |
| Isoflurane           | 6.55±2.78  | 7.0±2.06  | 8.11±1.16 |       |
| Sevoflurane          | 6.22±2.68  | 7.8±2.36  | 6.88±1.76 |       |
| **CO (L/min)**       |            |           |           |       |
| Isoflurane           | 5.18±1.13  | 5.10±0.98 | 8.11±1.26 | 0.323 |
| Sevoflurane          | 5.10±0.98  | 8.11±1.26 |       |       |
| **CI (L/min/m²)**    |            |           |           |       |
| Isoflurane           | 3.12±0.61  | 5.32±0.89 |       | 0.329 |
| Sevoflurane          | 2.84±0.68  | 5.01±0.73 |       |       |
| **SVR (dynes.sec/cm5)** |         |           |           |       |
| Isoflurane           | 1087±251   | 602±155  |       | 0.794 |
| Sevoflurane          | 980±178    | 677±134  |       |       |

Values are expressed as mean ± S.D. n = 9 in each group. MAP- Mean arterial pressure, CVP- Central venous pressure, CO- cardiac output, CI- Cardiac index, SVR- Systemic vascular resistance

---

**Figure 1**: Changes in CKMB values 12 hours post-operatively in patients administered sevoflurane or isoflurane. Values at 12 hours were subtracted from those after surgery to generate the data.

**Figure 2**: Malondialdehyde (a) and protein carbonyl (b) levels in the serum of isoflurane and sevoflurane subjects. The data is expressed as mean ± SEM, n = 8.*P < 0.05 when compared to sevoflurane group at one hour after coming off pump.
Nitric oxide is rapidly metabolized to stable end products such as nitrate, and this was measured in serum from patients undergoing CABG as an indicator of nitrosative stress. High levels of nitrate reflect increased NO levels and are generally damaging. As seen in Figure 4, there was no increase in nitrate levels after ischemia, or after reperfusion, suggesting that anesthetic preconditioning had a protective effect. The levels were lower in patients treated with sevoflurane when compared to the isoflurane group at both pre and post bypass periods. This suggests that sevoflurane provides better protection than isoflurane during these phases of CABG. This difference in levels between the two groups attained statistical significance ($P < 0.05$) for the two later time points.

**DISCUSSION**

It has been demonstrated earlier that sevoflurane selectively increased collateral flow to ischemic areas in the dogs with chronic LAD stenosis and De Hert and colleagues have shown significant decrease in ICU and hospital length of stay in the volatile groups (sevoflurane and desflurane) when compared with the non-volatile agents (Propofol and midazolam). Sevoflurane also appears to yield a better outcome, in terms of mortality and cardiac morbidity, in patients undergoing cardiac surgery. Studies on animal models have suggested that volatile anesthetics mediate their beneficial effect by modulation of oxygen free radicals and nitric oxide. Sevoflurane induced reduction of free radicals is partly dependent on the opening of ATP-sensitive K+ channels (K\textsubscript{ATP} channels). However, studies in humans examining modulation of oxidative and nitrosative stress by volatile anesthetics are scarce and this was examined in this study. Since it has been shown that discontinuation of anesthetics more than 30 min before occlusion of the coronary artery resulted in loss of the preconditioning effect, we decided to use the volatile agents throughout CPB and also post pump to achieve both early and late pre-conditioning effects.

No significant difference was evident between the patients treated with either isoflurane or sevoflurane in hemodynamic data or length of ICU stay. CK-MB was chosen as the cardiac biochemical marker since earlier pilot studies had shown that CK-MB was seen to rise within 4 to 8 hrs and peak at 18 hrs, while Troponin-I levels stayed elevated for 7 to 10 days once elevated. Since this rapid rise and fall of CK-MB would better reflect rapid changes in myocardial function which may not be evident on measuring troponin-I, it was chosen as the myocardial marker. The data indicates that CK-MB values decreased at 12 hours post operatively in the majority of patients on sevoflurane, unlike the isoflurane group. A study comparing propofol and sevoflurane showed that while serum troponin-T and CK-MB concentrations

---

**Figure 4:** Nitrate levels in the serum of isoflurane and sevoflurane subjects. The data is expressed as mean ± SEM, $n=8$. *$P < 0.05$ when compared to sevoflurane at one hour after cross clamp and # $P < 0.05$ when compared to sevoflurane group at one hour after coming off pump.

**Table 2b: CPB duration and ICU stay**

|                 | Group 1       | Group 2       | $P$   |
|----------------|--------------|--------------|------|
| CPB Dn (hrs)   | 1.5±0.02     | 2±0.02       | 0.799|
| ICU stay (hrs) | 21.7±6.86    | 19.0±2.52    | 0.303|

Values are expressed as mean±S.D. $n=9$ in each group. CPB Dn- Cardiopulmonary bypass duration, ICU- Intensive care unit
increased significantly in both groups from 60 minutes after declamping the aorta the increase was lesser in the sevoflurane group.\textsuperscript{[21]} Choi et al. demonstrated that the remote ischemic preconditioning reduced the myocardial injury by measuring low levels of serum CK-MB release in a complex valvular cardiac surgical patients.\textsuperscript{[22]} Even though Hemmerling et al. study didn’t show any changes in cardiac indices and contractility between sevoflurane and isoflurane groups in off-pump cardiac surgery, it revealed patients treated with sevoflurane recovered rapidly from anesthesia.\textsuperscript{[23]}

The role of oxygen free radicals in mediating the beneficial effects of volatile anesthetics pre-conditioning have been well studied in animal models. A study examining effects of isoflurane and sevoflurane in a warm liver ischemia-reperfusion (IR) model in the rat showed that tissue malondialdehyde levels were significantly low in the sevoflurane group compared with the isoflurane group.\textsuperscript{[24]} Sevoflurane administration also resulted in lesser plasma malondialdehyde levels when compared to desflurane in a study examining oxidative status during general anesthesia in mechanically ventilated swine.\textsuperscript{[25]}

In humans, our data indicate that in cardiac pulmonary bypass surgeries, both isoflurane and sevoflurane prevent increase in malondialdehyde levels; sevoflurane having a better effect at both the pre and post bypass time points. Both agents were also effective against protein oxidation when used during CPB. The increase in plasma malondialdehyde levels was also found to be prevented by administration of sevoflurane when compared to desflurane in a study of patients undergoing elective laparoscopic cholecystectomy.\textsuperscript{[26]} In a study examining patients undergoing laparoscopic abdominal surgery it was seen that Sevoflurane and desflurane showed a protective effect against the increase in malondialdehyde and protein carbonyl levels peri-operatively.\textsuperscript{[27]} Sevoflurane preconditioning mitigates the ischemia-reperfusion injury and improves the cardiac function.\textsuperscript{[28-30]} Erturk et al. observed that sevoflurane provides better protection from ischemic reperfusion injury in thoracic surgical patients after one lung ventilation compared to propofol by lower rise in malondialdehyde and ischemia modified albumin levels during the perioperative period.\textsuperscript{[31]}

Thiols have important functions as anti-oxidants and loss of thiols is generally an evidence of oxidative stress. Glutathione is an important thiol anti-oxidant and intensification of intracellular glutathione (GSH) depletion in neutrophils has been demonstrated with the presence of sevoflurane in vitro.\textsuperscript{[32]} It has also been shown that serum protein sulphydryl levels were found to be decreased in patients undergoing laparoscopic cholecystectomy.\textsuperscript{[33]} In a recent study by Ozcan et al. it has shown that sevoflurane has a better protective effect on thiol-disulphide homeostasis than desflurane.\textsuperscript{[34]} Our data indicates that in patients undergoing CABG, there are alterations in both serum total and protein thiols, and sevoflurane has a protective effect in thiol maintenance. Nitric oxide production has been shown to be altered in coronary artery bypass surgery, with NO production being more prominent in off-pump than in on-pump coronary artery bypass surgery.\textsuperscript{[35]} Plasma nitrate levels showed a significant increase 30 min after CPB commencement and 10 min after the end of CPB.\textsuperscript{[36]} These changes seem to have been blunted in our study, probably because of volatile anesthetics used. Lee et al. demonstrated in rats that pretreatment with volatile anesthetics reduced the levels of nitric oxide and malondialdehyde.\textsuperscript{[37]} Sevoflurane at 2.4 Mac lowered NO levels in renal interstitial fluid when administered to dogs,\textsuperscript{[38]} and a decrease in plasma NO levels has been shown at the end of surgery in patients undergoing elective major surgery who received sevoflurane or other inhalational anesthetics.\textsuperscript{[39]}

Limitations

Even though our study encourages to use volatile anesthetics particularly sevoflurane, there were limitations. First of all our sample size was small and we didn’t have a control group without volatile anesthetics to prove that inhalational anesthetics are superior to intravenous agents. A control arm with no or low preconditioning effect could have improved the power of this study. Since these patients were not followed up after their discharge from the hospital, the long term clinical benefits cannot be commented.

CONCLUSION

From our study, it can be concluded that preconditioning with both volatile anesthetics, Isoflurane and Sevoflurane prevent oxidative and nitrosative stresses during CABG. Between the two agents, Isoflurane seems to provide better protection during the pre-cardiopulmonary bypass period, while Sevoflurane provides protection during both pre- as well as post-cardiopulmonary bypass periods.

Acknowledgements

The Wellcome Trust Research Laboratory is supported by the Wellcome Trust, London. Funding for this study was from the Christian Medical College Fluid Research Fund. The authors thank Professor KA Balasubramanian for useful discussions and members of the Department of Cardiothoracic Surgery for technical assistance.
Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Heindl B, Reichle FM, Zahler S, Conzen PF, Beeker BF. Sevoflurane and isoflurane protect the perfused guinea pig heart by reducing postischemic adhesion of polymorphonuclear neutrophils. Anesthesiology 1999;91:521-30.

2. Kowalski C, Zahler S, Beeker BF, Flaucher A, Conzen PF, Gerlach E, et al. Halothane, isoflurane, and sevoflurane reduce postischemic adhesion of neutrophils in the coronary system. Anesthesiology 1997;86:188-95.

3. Kersten JR, Schmelting T, Tressmer J, Hettreich DA, Pagel PS, Wartler DC. Sevoflurane selectively increases coronary collateral blood flow independent of KATP channels in vivo. Anesthesiology 1999;90:246-56.

4. Symons JA, Myles PS. Myocardial protection with volatile anaesthetic agents during coronary artery bypass surgery: A meta-analysis. Br J Anaesth 2006;97:127-36.

5. Kevin LG, Novalija E, Stowe DF. Reactive oxygen species as mediators of cardiac injury and protection: The relevance to anesthesia practice. Anesth Analg 2005;101:1275-87.

6. Novalija E, Varadarajan SG, Camara AKS, An J, Chen Q, Riess ML, et al. Anesthetic preconditioning: Triggering role of reactive oxygen and nitrogen species in isolated hearts. Am J Physiol Heart Circ Physiol 2002;283:H44-52.

7. Hanouz J-L, Zhu L, Lemoine S, Durand C, Lepage O, Massetti M, et al. Reactive oxygen species mediate sevoflurane- and desflurane-induced preconditioning in isolated human right atria in vitro. Anesth Analg 2007;105:1534-9, table of contents.

8. Bouwman RA, Musters RJP, van Beek-Harmsen BJ, de Lange JJ, Lamberts RR, Loer SA, et al. Reactive oxygen species undergoing free radical reactions are involved in postischemic adhesion of polymorphonuclear neutrophils during coronary artery bypass surgery. Br J Anaesth 2007;99:639-45.

9. Kevin LG, Novalija E, Riess ML, Camara AKS, Rhodes SS, Stowe DF. Sevoflurane exposure generates superoxide but leads to decreased superoxide during ischemia and reperfusion in isolated hearts. Anesth Analg 2003;96:949-55, table of contents.

10. Nakamuru K, Al-Ruzeh S, Gray C, Yacoub M, Amrani M. Effect of myocardial reperfusion on the release of nitric oxide after regional ischemia: An experimental model of beating-heart surgery. Tex Heart Inst J 2006;33:35-9.

11. Tessier-Vezdel D, Tissier R, Wahtauir X, Ghaleh B, Berdeaux A, et al. Comparison of the effects of sevoflurane and desflurane on oxidative stress in patients undergoing coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 2006;20:503-8.

12. Choi YS, Shim JK, Kim JC, Kang K-S, Seo YH, Ahn K-R, et al. Effect of remote ischemic preconditioning on renal dysfunction after complex valvular heart surgery: A randomized controlled trial. J Thorac Cardiovasc Surg 2011;142:148-54.

13. Hammerling T, Olivier J-F, Le N, Prieto I, Bracco D. Myocardial protection by isoflurane vs. sevoflurane in ultra-fast-track anesthesia for off-pump aortocoronary bypass grafting. Eur J Anaesthesiol 2008;25:230-6.

14. Bedirli N, Öhaoglu E, Kerem M, Uteby G, Alper M, Yilmazer D, et al. Hepatic energy metabolism and the differential protective effects of sevoflurane and isoflurane anesthesia in a rat hepatic ischemia-reperfusion injury model. Anesth Analg 2008;106:830-7, table of contents.

15. Allaouchiche B, Debon R, Goudable J, Chassard D, Dulfo F. Oxidative stress status during exposure to propofol, sevoflurane and desflurane. Anesth Analg 2001;93:981-5.

16. Koksal GM, Sayilgan C, Aydin S, Uzun H, Oz H. The effects of sevoflurane and desflurane on lipid peroxidation during laparoscopic cholecystectomy. Eur J Anaesthesiol 2004;21:217-20.

17. De Hert SG, Van der Linden PJ, Cromheecke S, Meeus R, ten Broecke PW, De Blier JG, et al. Choice of primary anesthetic regimen can influence intensive care unit length of stay after coronary surgery with cardiopulmonary bypass. Anesthesia 2004;101:9-20.

18. Landoni G, Fochi O, Torri G. Cardiac protection by volatile anaesthetics: A review. Curr Vase Pharmacol 2008;6:108-11.

19. Deng J, Lei C, Chen Y, Fang Z, Yang Q, Zhang H, et al. Neuroprotective gases—fantasy or reality for clinical use? Prog Neurobiol 2014;115:210-45.

20. De Hert SG, Turani F, Mathur S, Stowe DF. Cardioprotection with volatile anaesthetics: Mechanisms and clinical implications. Anesth Analg 2005;100:1584-93.

21. Kawamura T, Kadosaki M, Nara N, Kaise A, Suzuki H, Endo S, et al. Effects of sevoflurane on cytokine balance in patients undergoing coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 2006;20:503-8.

22. Choi YS, Shim JK, Kim JC, Kang K-S, Seo YH, Ahn K-R, et al. Effect of remote ischemic preconditioning on renal dysfunction after complex valvular heart surgery: A randomized controlled trial. J Thorac Cardiovasc Surg 2011;142:148-54.

23. Hammerling T, Olivier J-F, Le N, Prieto I, Bracco D. Myocardial protection by isoflurane vs. sevoflurane in ultra-fast-track anesthesia for off-pump aortocoronary bypass grafting. Eur J Anaesthesiol 2008;25:230-6.

24. Bedirli N, Öhaoglu E, Kerem M, Uteby G, Alper M, Yilmazer D, et al. Hepatic energy metabolism and the differential protective effects of sevoflurane and isoflurane anesthesia in a rat hepatic ischemia-reperfusion injury model. Anesth Analg 2008;106:830-7, table of contents.
cholecystectomy. Eurasian J Med 2019;51:70-4.

35. Mitaka C, Yokoyama K, Imai T. Nitric oxide production is more prominent in off-pump than in on-pump coronary artery bypass surgery. Anaesth Intensive Care 2007;35:505-9.

36. Ruvolo G, Speziale G, Greco F, Tritapepe L, Mollace V, Nistico G, et al. Nitric oxide release during hypothermic versus normothermic cardiopulmonary bypass. Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg 1995;9:651-4.

37. Lee Y-M, Song BC, Yeum K-J. Impact of volatile anesthetics on oxidative stress and inflammation. BioMed Res Int 2015;2015:242709. doi: 10.1155/2015/242709.

38. Kusudo K, Ishii K, Rahman M, Aki Y, Miyatake A, Kosaka H, et al. Blood flow-dependent changes in intrarenal nitric oxide levels during anesthesia with halothane or sevoflurane. Eur J Pharmacol 2004;498:267-73.

39. Delogu G, Antonacci A, Signore M, Marandola M, Tellan G, Ippoliti F. Plasma levels of IL-10 and nitric oxide under two different anaesthesia regimens. Eur J Anaesthesiol 2005;22:462–6.