Cardiac Protection With Volatile Anesthetics in Stenting Procedures

Giovanni Landoni, MD,* Alberto Zangrillo, MD,* Oliviero Fochi, MD,* Giulia Maj, MD,*
Anna Mara Scandroglio, MD,* Andrea Morelli, MD,† Luigi Tritapepe, MD,† Matteo Montorfano, MD,‡
and Antonio Colombo, MD‡

Objective: **Myocardial ischemic damage is reduced by volatile anesthetics in patients undergoing coronary artery bypass graft surgery. The authors tested the hypothesis that low-dose sevoflurane could decrease perioperative myocardial damage, as measured by cTnI release, when compared with placebo, in patients undergoing interventional cardiology procedures.**

Design: **A single-blind, randomized controlled trial.**

Setting: **A university hospital.**

Participants: **Thirty patients undergoing stenting procedures (May 2005) were included in the present study.**

Interventions: **The authors randomly assigned 16 patients to breathe sevoflurane (expired end-tidal concentration 1%) and 14 patients to breathe a placebo oxygen/air mix before stenting procedures.**

Measurements and Main Results: **Postprocedural cardiac troponin I release was measured as a marker of myocardial necrosis. Sixteen patients had detectable cardiac troponin I levels after stenting procedures, with no difference between groups: 10 in the sevoflurane group (16 patients) versus 6 in the placebo group (14 patients) ($p = 0.3$). No difference in the amount of postprocedural median (interquartile range) cardiac troponin I release was noted between the sevoflurane group, 0.15 (0-4.73) ng/mL, and the placebo group, 0.14 (0-0.87) ng/mL ($p = 0.4$).**

Conclusions: **Myocardial damage measured by cardiac troponin release was not reduced by the volatile anesthetic sevoflurane during interventional cardiology procedures in this study.**

KEY WORDS: inhalation anesthetics, myocardial preconditioning, myocardial ischemia, coronary stenting

IN THE SETTING OF percutaneous[1] and surgical[2] revascularization, patients showing postprocedural elevation in cardiac troponin (cTn) have evidence of new irreversible myocardial injury on delayed-enhancement magnetic resonance imaging. The magnitude of this injury correlates directly with the extent of cTn elevation and predicts short- and long-term outcomes after stenting procedures[1,3] and coronary artery bypass graft (CABG) surgery.[4] There is no discernible threshold below which an elevated value for cTn would be deemed harmless.[5]

The potential benefits of reducing cardiac damage have led to a renewed interest in cardiac protection strategies, including pharmacologic preconditioning.[6] Volatile anesthetics, commonly used in general anesthesia to induce and maintain hypnosis, analgesia, amnesia, and mild muscle relaxation, improve postischemic recovery at the cellular level in isolated hearts and in animals mainly through pharmacologic preconditioning.[7] A reduced release of cTn in patients receiving newer volatile anesthetics (desflurane or sevoflurane) as a part of their anesthesia plan has been documented after cardiac surgery, along with reduced incidences of perioperative myocardial infarction and death.[8] These cardioprotective effects were documented even when volatile anesthetics were administered for less than 20 minutes.[9-11]

In the present randomized controlled study, the authors tested the hypothesis that subminimum alveolar concentration (MAC) doses of sevoflurane could decrease perioperative myocardial damage, as measured by cTnI release, when compared with placebo in patients undergoing interventional cardiology procedures.

METHODS

The study was performed according to the principles of the Declaration of Helsinki. The ethical committee approved the study, and written informed consent was obtained from each patient. Consecutive patients scheduled for elective interventional cardiology procedures were randomly assigned to breathe volatile anesthetics or placebo before stenting procedures.

All subjects undergoing stenting procedures were eligible if they were older than 18 years. Patients were excluded if they experienced myocardial infarction during the preceding 6 weeks, had preprocedural measurable cTnI, active congestive heart failure, any surgical procedure during current admission, previous unusual response to an anesthetic, or used any experimental drug within 28 days before surgery. Patients taking sulfonylureas, theophylline, or allopurinol were also excluded because these drugs inhibit pharmacologic preconditioning.

All patients were kept NPO for 8 hours. A peripheral venous access catheter was positioned. Monitoring included noninvasive blood pressure, continuous electrocardiographic leads II and V_5 with ST-segment monitoring, pulse oximetry, end-tidal CO_2, and end-tidal sevoflurane concentration.

All patients were requested to breathe spontaneously in a tight-fitting, occlusive mask (held by the anesthesiologist) in which oxygen 50% and air (fresh gas flow = 12 L) were delivered through a mask connected to the breathing circuit and gas-scavenging system of a Draeger anesthesia machine (Drager, Lubeck, Germany).

Randomization was carried out, and the details of the randomization were contained in a set of sealed envelopes. Of the 37 eligible patients, 7 refused to sign the consent and did not take part in the study.

Patients in the volatile anesthetic group breathed sevoflurane (Sevorane; Abbott, North Chicago, IL) titrated to reach 0.5 end-tidal MAC (1%) for 20 minutes. Patients in the placebo group simply breathed oxygen and air. No sedation or analgesia was given to this group of patients as per hospital protocol. At the end of the 20 minutes, the patients entered into the washout period, spontaneously breathing air. The procedure was performed in the recovery room of the cardiology laboratory by an anesthesiologist. Ten minutes after the washout period, patients were transferred to the cardiology laboratory. Sevoflu-

*From the *Department of Cardiothoracic Anesthesia and Intensive Care and ‡Laboratory of Interventional Cardiology, Università Vita-Salute San Raffaele e Istituto Scientifico San Raffaele, Milan, Italy; and †Dipartimento di Scienze Anestesiologiche, Medicina Critica e Terapia del Dolore, Università degli Studi "La Sapienza" di Roma, Rome, Italy.*

G.L. and L.T. received reimbursement for conferences-simposia and L.T. received an honoraria for writing a CD on sevoflurane.

Address reprint requests to Giovanni Landoni, MD, Department of Cardiothoracic Anesthesia and Intensive Care, Istituto Scientifico San Raffaele, via Olgettina 60, 20132 Milan, Italy. E-mail: landoni.giovanni@hsr.it

1053-0770/08/2204-0006$34.00/0
doi:10.1053/j.jvca.2008.02.020

Table 1. Data of 30 Patients Who Received 20 Minutes of 1% End-Tidal Sevoflurane (16 Patients) or Placebo (14 Patients) Through a Mask in Which Oxygen and Air Were Delivered Before Stenting Procedures

	Placebo (14 Patients)	Sevoflurane (16 Patients)	*p* Value
Preoperative data			
Age (y)	68 ± 9.7	69 ± 10.2	0.4
Weight (kg)	77 ± 12.5	75 ± 11.1	0.6
Height (cm)	168 ± 4.4	167 ± 7.3	0.6
BMI	26.9 ± 3.9	26.5 ± 2.6	0.8
Diabetes, n (%)	3 (21.4)	2 (12.5)	0.4
Hypertension, n (%)	14 (100)	12 (75)	0.07
Chronic renal dysfunction, n (%)	2 (14.3)	0 (0)	0.2
Dyslipidemia, n (%)	13 (92.9)	13 (81.3)	0.7
Peripheral vasculopathy, n (%)	2 (14.3)	2 (12.5)	0.6
Smoker, n (%)	3 (21.4)	9 (56.3)	0.1
Previous myocardial infarction, n (%)	9 (64.3)	7 (43.8)	0.6
Previous percutaneous coronary intervention, n (%)	7 (50)	7 (43.8)	0.9
Previous coronary artery bypass graft, n (%)	3 (21.4)	6 (37.5)	0.15
Coronary artery disease familiarity, n (%)	3 (21.4)	6 (37.5)	0.3
Ejection fraction (%)	47 ± 11	45 ± 10	0.6
NYHA, n (%)			
I	3 (21)	4 (25)	
II	6 (43)	7 (44)	
III	5 (36)	5 (31)	
Medications			
β-blockers, n (%)	6 (42.9)	9 (56.3)	0.13
Calcium antagonists, n (%)	2 (14.3)	3 (18.8)	0.6
Diltiazem, n (%)	3 (21.4)	4 (25)	0.6
Angiotensin II antagonists, n (%)	3 (21.4)	2 (12.5)	0.4
ACE inhibitors, n (%)	3 (21.4)	10 (62.5)	0.06
Statins, n (%)	11 (78.6)	15 (93.8)	0.2
Clopidogrel, n (%)	2 (14.3)	3 (18.8)	0.6
Ticlopidine, n (%)	6 (42.9)	12 (75)	0.15
Antiplatelets, n (%)	11 (78.6)	16 (100)	0.08
Digoxin, n (%)	2 (14.3)	0 (0)	0.7
Insulin, n (%)	3 (21.4)	0 (0)	0.08
Furosemide, n (%)	3 (21.4)	2 (12.5)	0.4
Hydrochlorothiazide, n (%)	1 (7.1)	2 (12.5)	0.6
Spironolactone, n (%)	1 (7.1)	1 (6.3)	0.7
Omega 3, n (%)	2 (14.3)	6 (37.5)	0.15
Operative procedures and postoperative data			
No. of stents	1.5 ± 0.73	1.4 ± 0.76	0.9
Patients undergoing angioplasty on top of coronary stenting (%)	5 (31)	3 (21)	0.4
cTnI (ng/mL), median (interquartile range)	0.15 (0-4.73)	0.14 (0-0.87)	0.4

Abbreviation: BMI, body mass index.

rane was chosen for its known beneficial effects on postischemic mechanical and coronary function and because it is not an irritant for the respiratory system of the awake patient. The authors chose to administer it for 20 minutes because the cardioprotective effects of volatile anesthetics were documented even when administered for less than 20 minutes.[9,11,12] The authors chose to administer 1% sevoflurane because in 9 trials identical (0.5 MAC) or lower concentrations of volatile anesthetics were used.[8]

End-tidal carbon dioxide concentration was allowed to increase to 40 mmHg in the placebo group and to 50 mmHg in the treatment group. The respiratory rate was allowed to range from 10 to 20 per minute.

In the present study, the authors tested the hypothesis that the volatile anesthetic sevoflurane given before stenting procedures would reduce perioperative myocardial damage, as assessed by postoperative cTnI release, when compared with placebo. The primary endpoint of the study was the postprocedural release of cTnI.

Baseline demographics, clinical characteristics, and periprocedural data were collected by trained blinded observers who did not participate in patient care (Table 1). According to current interventional practice,[13] percutaneous coronary intervention with balloon inflation and stent implantation entails the transitory occlusion of blood flow to distal myocardial regions for an average of 10 to 60 seconds for each treated lesion. However, the ischemic time varies widely depending on the complexity of the procedure, and its effect is modulated by the whole amount of myocardium at risk.

Percutaneous coronary intervention (PCI) with stent implantation was performed according to standard guidelines[14] by a single cardiologist. Specifically, the target lesion was wired with a 0.014-inch guidewire, predilated when necessary, and stent implantation was performed with a balloon-to-artery ratio of 1.1/1.0 at a moderate-to-high pressure (12-18 atm). The authors administered periprocedural unfractioned heparin according to body weight (target activated coagulation time

>275 seconds), and dual antiplatelet therapy was started before or during PCI and continued for 1 to 6 months.

The authors drew blood samples to determine cTnI concentrations twice for each patient: once before the procedure and once 18 hours after coronary stenting before patient discharge. Blood was collected in plastic tubes with clot activator (Becton Dickinson Vacutainer Systems; Becton Dickinson, Plymouth, UK) and was centrifuged (2,500*g* for 15 minutes) before analysis. CTnI was assayed with Dimension XPand (Dade-Behring Diagnostic, Paris, France) according to the manufacturer's instructions. The cTnI method is a 1-step enzyme immunoassay based on the sandwich principle. Sensitivity of the assay is 0.04 ng/mL.

Sample-size calculations were based on a 2-sided alpha error of 0.05 and 80% power. On the basis of previous data,[5] the authors anticipated a 60% frequency of patients releasing cTnI in the standard treatment group and assumed a 50% reduction after treatment with sevoflurane. At least 6 randomized trials have indeed already shown a greater than 50% reduction in cTnI release in patients receiving volatile anesthetics for cardiac surgery,[15-17] in particular off-pump CABG (OPCAB) surgery.[18,19]

The authors calculated that a sample size of 47 patients per group would be needed. Therefore, the total study population was 94. The first of the 2 planned ad interim analyses was performed after 30 patients were included in the protocol following the suggestion of De Mets et al,[20] with the 95% confidence intervals based on the Wilson score for the difference between independent proportions as explained by Newcombe.[21] This analysis showed that no 50% reduction in the number of patients releasing cTnI was to be expected at the end of the study.

In this case, some authors suggest continuing despite a null or adverse finding in order to provide more conclusive evidence against the new therapy. The documented nonefficacy of sevoflurane in reducing the percentage of patients releasing cTnI and the safety concerns because of periprocedural side effects (1 case of mild respiratory depression that was easily managed by the attending anesthesiologist in 1 sevoflurane patient, and involuntary muscular contractions that mimicked seizures in another, which were later discovered to be a peculiar sleep characteristic of the patient) persuaded the authors to terminate the study.

Data were stored electronically and analyzed by use of Epi Info 2002 software (Centers for Disease Control) and SAS software, version 8 (SAS Institute, Cary, NC). All data analysis was performed according to a pre-established analysis plan. Dichotomous data were compared by using 2-tailed chi-square test with the Yates correction or Fisher exact test when appropriate. Continuous measures were compared by a Mann-Whitney *U* test. Two-sided significance tests were used throughout. Data are presented as median (interquartile range) or as mean (± standard deviation) if not otherwise indicated.

RESULTS

In May 2005, 30 consecutive qualifying and consenting patients were randomly assigned to receive either the volatile anesthetic sevoflurane (16 patients) or placebo (14 patients).

The baseline demographic and clinical characteristics of the 2 groups are summarized in Table 1. No statistically significant preprocedural differences were noted. There was a trend toward more patients on antiplatelets and angiotensin-converting enzyme inhibitors in the sevoflurane group and a trend toward more hypertensive patients and patients on insulin in the placebo group.

The number of stented vessels was similar in the 2 groups (1.5 ± 0.73 *v* 1.4 ± 0.76, $p = 0.9$). Five patients (31%) in the sevoflurane group and 3 patients (21%) in the control group also underwent angioplasty ($p = 0.4$).

Table 2. Postoperative cTnI Levels

Sevoflurane Pt	TnI (ng/mL)	Placebo Pt	TnI (ng/mL)
1	<0.04	1	0.87
2	0.05	2	<0.04
3	0.15	3	<0.04
4	0.22	4	0.14
5	<0.04	5	0.14
6	6.19	6	0.14
7	0.09	7	<0.04
8	0.15	8	<0.04
9	0.04	9	2.42
10	4.73	10	0.14
11	1.27	11	<0.04
12	<0.04	12	0.18
13	0.44	13	1.04
14	14.60	14	0.75
15	<0.04		
16	5.03		
Median	0.15		0.14
IQR	0-4.73		0-0.87

NOTE. Sensitivity of the assay used by the authors' laboratory is 0.04 ng/mL.

Abbreviations: Pt, patient number; TnI, troponin I; IQR, interquartile range.

Systolic arterial blood pressure was similar at baseline in the sevoflurane and control groups (145 ± 17 *v* 146 ± 19 mmHg), but was reduced during sevoflurane inhalation (129 ± 16 *v* 140 ± 16 mmHg after 20 minutes of sevoflurane, $p = 0.06$). No patient experienced hypotension, defined as a reduction in systolic arterial blood pressure >30 mmHg.

Sixteen patients had detectable cTnI after stenting procedures with no differences between groups: 10 (62%) in the sevoflurane group (16 patients) versus 6 (43%) in the placebo group (14 patients, $p = 0.3$, Table 2). No differences in the amount of postprocedural median (interquartile range) cTnI release was noted between the sevoflurane group, 0.15 (0-4.73) ng/mL, and the placebo group, 0.14 (0-0.87) ng/mL ($p = 0.4$).

All patients in the treatment group received 1% end-tidal sevoflurane, slept while breathing this concentration of volatile anesthetic, woke up immediately after sevoflurane discontinuation, and did not show confusion, anxiety, or apprehension during the procedure. Patients in the control group did not sleep during air-oxygen administration. No patients had abnormal values in end-tidal carbon dioxide concentration or in respiratory rate.

In the sevoflurane group, 1 mild respiratory depression (dose-dependent effect of the volatile anesthetic) was easily managed by the attending anesthesiologist (brief interruption of sevoflurane administration and ventilation through a self-inflating breathing bag for 1 minute); the patient had an uneventful periprocedural course, and no detectable cTnI was found. He was not given other sedative drugs before the study protocol and at the moment of the transient hypoventilation had an end tidal concentration of sevoflurane = 1%. Involuntary muscular contractions were noted in another patient in the sevoflurane group; these were later discovered to be a peculiar sleep characteristic of this patient. All patients had an uneventful periprocedural course and were discharged within 48 hours.

DISCUSSION

The most important result of this study is that patients receiving low-dose sevoflurane as a pharmacologic preconditioning agent before interventional cardiology procedures have no reduction in myocardial damage compared with patients receiving placebo.

This is the first trial to investigate the effect of volatile anesthetics in patients undergoing interventional cardiology procedures, whereas data are accumulating in favor of the cardioprotective effects of volatile anesthetics in cardiac surgery. Existing evidence has recently been summarized by a meta-analysis.[8] The authors pooled data regarding the use of desflurane and sevoflurane in 22 trials and 1,922 patients, finding significant reductions of in-hospital mortality (4/977 [0.4%] in the volatile anesthetics group *v* 14/872 [1.6%] in the total intravenous arm, operating room [OR] = 0.35 [0.14-0.90], *p* for effect = 0.003, *p* for heterogeneity = 0.98, I^2 = 0%), myocardial infarction rate (24/979 [2.4%] *v* 45/874 [5.1%], OR = 0.53 [0.32-0.86], *p* for effect = 0.001, *p* for heterogeneity = 0.93, I^2 = 0%), intensive care unit and hospital stay, time on mechanical ventilation, and incidence of long-term cardiac events. In 4 of these trials, volatile anesthetics were administered for less than 20 minutes,[9-12] and in 9 trials identical (0.5 MAC) or lower concentrations were used.[8]

The authors decided to use the most recently described and preferred biomarker for myocardial damage, cTnI, which has nearly absolute myocardial specificity as well as high sensitivity, thereby reflecting even microscopic zones of myocardial necrosis. cTnI is detectable a few hours after myocardial damage, and it peaks within the first day.[5]

The mechanisms underlying the benefits of volatile anesthetics are not completely clear; however, they protect the myocardium by mechanisms that are similar to ischemic preconditioning, with the clear advantage of not requiring ischemia to produce this effect. In 1986, Murry et al[22] found that brief cycles of left circumflex coronary artery occlusion reduced the size of myocardial infarction by 75% after a subsequent 40-minute occlusion. This phenomenon, named "ischemic preconditioning," has been extensively investigated[23]; short ischemia and reperfusion preconditioning stimuli trigger a signaling cascade of intracellular events and thus create a memory effect that attenuates ischemia-reperfusion injury. Improving knowledge of the basic mechanisms involved in myocardial preconditioning has prompted clinicians to propose alternative methods in order to achieve the cardioprotective benefit without inducing myocardial ischemia. Several studies have shown a similar effect of volatile anesthetics in protecting the myocardium from ischemia-reperfusion injury.[6] In a way similar to ischemic preconditioning, volatile anesthetics can trigger an acute cardioprotective memory effect that lasts beyond their elimination,[23] called "anesthetic or pharmacologic preconditioning." Volatile anesthetics have been used with success for decades and could play a useful role when patients with coronary artery disease need to undergo surgery. Volatile anesthetics also have effects that may contribute to protection when administered after the onset of ischemia, such as mitigation of Ca^{2+} overload, free-radical production, and neutrophil adhesion.[7]

The reduction in cTn release with the use of volatile anesthetics has been shown in OPCAB,[18,24] a surgical intervention that is somewhat similar to coronary artery stenting in terms of mechanisms and magnitude of myocardial damage. Both procedures entail a brief occlusion of the coronary artery that is to be bypassed or stented, thus causing ischemia in a predictable area of the myocardium, and they represent 2 of the few controlled models of human myocardial ischemia. This offers the opportunity to study preventive measures that, if effective, could be transferred to all patients undergoing procedures at risk for ischemia and myocardial damage.

Conzen et al,[24] in a small study (20 patients), showed for the first time that cTnI concentration increased more after a total intravenous anesthesia than after volatile anesthesia. Bein et al[25] found echocardiographic evidence of preserved myocardial function in the volatile anesthetic group when compared with total intravenous anesthesia in patients undergoing brief periods of ischemia during OPCAB but found no difference in cardiac Tn levels. Guarracino et al[18] showed a reduction of cTnI release in patients receiving volatile anesthetics in a multicentric experience.

The cardioprotective properties of halogenated anesthetics have been shown to be dependent also on the modalities of their administration.[26] To the best of the authors' knowledge, this is the first study to investigate the use of volatile anesthetics in coronary stenting procedures, and no comparisons can be made with other preconditioning protocols in this specific setting.

Although similar doses of volatile anesthetics and even shorter times of administration have been shown to reduce cTnI release in cardiac surgery, it is possible that the combination of low doses and short times do not permit proper pharmacologic preconditioning in this setting. It is also possible that different mechanisms of cardiac damage exist between cardiac surgery and stenting procedures. A wide disparity in study design, quality, endpoints, and variability in cTnI levels exist in published articles so far.

In this study, the amount of sevoflurane may have been inadequate. Even if higher doses and time of administration could have given different results, in the present study, the possibility to induce general anesthesia with a laryngeal mask in order to attain higher concentration in a safe and reliable manner was not considered in the setting of a noninvasive procedure because of the costs and risks for hemodynamic and respiratory instability. The administration of sevoflurane 0.5% is time-consuming and requires an anesthesiologist to be present, mainly for the risk of respiratory depression. Administering sevoflurane throughout the procedure could be investigated in the future.

Since the sample size was small because of the premature interruption of the trial after the first ad interim analysis, the authors showed that with 95% confidence a 50% reduction in cTnI release could not be expected if all 94 patients would have been randomized.

The duration of vessel occlusion during the stenting was also brief. Ischemic times and number of occlusions were not collected, and no relationship between ischemic times and troponin release was demonstrated. This study was not adequately powered to detect ischemia or myocardial infarction. It was powered on cTnI release because at least 6 randomized trials have already shown a greater than 50% reduction in cTnI release in patients receiving volatile anesthetics for cardiac surgery,[15-17] in particular for OPCAB surgery.[18,19] Single-point cTnI could be an

insensitive method to show differences in infarct size and therefore protection from any agent. A multipoint cTnI sampling could have shown increased sensitivity to the effect of treatment.

This procedure may not be equivalent to what occurs during CABG surgery. The authors acknowledge that there are several differences between OPCAB and PCI including the degree of inflammatory reaction, hemodynamic instability, and usual duration of occlusion (5-15 minutes instead of 10-60 seconds), which make these 2 procedures different and could explain different effects of sevoflurane.

This is the first trial to study the administration of volatile agents before stenting procedures as 1 factor that may affect myocardial ischemia. However, the authors did not observe any difference in myocardial damage as documented by cTnI release when compared with patients receiving placebo. This study provides evidence for the nonusefulness of volatile anesthetics in stenting procedures. Even if volatile anesthetics have low costs and cardioprotective properties during cardiac surgical procedures, the results of this study do not support their use in patients undergoing stenting procedures.

REFERENCES

1. Selvanayagam JB, Porto I, Channon K, et al: Troponin elevation after percutaneous coronary intervention directly represents the extent of irreversible myocardial injury: Insights from cardiovascular magnetic resonance imaging. Circulation 111:1027-1032, 2005

2. Selvanayagam JB, Pigott D, Balacumaraswami L, et al: Relationship of irreversible myocardial injury to troponin I and creatine kinase-MB elevation after coronary artery bypass surgery: Insights from cardiovascular magnetic resonance imaging. J Am Coll Cardiol 45:629-631, 2005

3. Giannitsis E, Muller-Bardorff M, Lehrke S, et al: Admission troponin T level predicts clinical outcomes, TIMI flow, and myocardial tissue perfusion after primary percutaneous intervention for acute ST-segment elevation myocardial infarction. Circulation 104:630-635, 2001

4. Lehrke S, Steen H, Sievers HH, et al: Cardiac troponin T for prediction of short- and long-term morbidity and mortality after elective open heart surgery. Clin Chem 50:1560-1567, 2004

5. Alpert JS, Thygesen K, Antman E, et al: Myocardial infarction redefined—A consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol 36:959-969, 2000

6. Piriou V, Chiari P: Con: Ischemic preconditioning is not necessary because volatile agents accomplish it. J Cardiothorac Vasc Anesth 18:803-805, 2004

7. Kato R, Foëx P: Myocardial protection by anesthetic agents against ischemia-reperfusion injury: An update for anesthesiologists. Can J Anesth 49:777-791, 2002

8. Landoni G, Biondi-Zoccai GGL, Zangrillo A, et al: Desflurane and sevoflurane in cardiac surgery: A meta-analysis of randomized clinical trials. J Cardiothorac Vasc Anesth 21:502-511, 2007

9. Julier K, da Silva R, Garcia C: Preconditioning by sevoflurane decreases biochemical markers for myocardial and renal dysfunction in coronary artery bypass graft surgery: A double-blinded, placebo-controlled, multicenter study. Anesthesiology 98:1315-1322, 2003

10. Frassdorf J, Weber NC, Borowski A, et al: Sevoflurane-induced preconditioning in men: 1 MAC for 5 min does not influence the phosphorylation of protein kinase C-e in right atrial myocardium. Anesthesiology 101:A286, 2004 (abstr)

11. Guarracino F, Doroni L, Cariello C, et al: Cardiac protection is a clinical evidence. Minerva Anestesiol 70:261-265, 2004

12. Nader ND, Li CM, Khadra WZ, et al: Anesthetic myocardial protection with sevoflurane. J Cardiothorac Vasc Anesth 18:269-274, 2004

13. Colombo A, Hall P, Nakamura S, et al: Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. Circulation 91:1676-1688, 1995

14. Briguori C, Colombo A, Airoldi F, et al: Statin administration before percutaneous coronary intervention: impact on periprocedural myocardial infarction. Eur Heart J 25:1822-1828, 2004

15. De Hert SG, Van der Linden PJ, Cromheecke S, et al: Choice of primary anesthetic regimen can influence intensive care unit length of stay after coronary surgery with cardiopulmonary bypass. Anesthesiology 101:9-20, 2004

16. De Hert SG, Cromheecke S, ten Broecke PW, et al: Effects of propofol, desflurane, and sevoflurane on recovery of myocardial function after coronary surgery in elderly high-risk patients. Anesthesiology 99:314-323, 2003

17. De Hert SG, ten Broecke PW, Mertens E, et al: Sevoflurane but not propofol preserves myocardial function in coronary surgery patients. Anesthesiology 97:42-49, 2002

18. Guarracino F, Landoni G, Tritapepe L, et al: Myocardial damage prevented by volatile anesthetics. A multicentre randomized controlled study. J Cardiothorac Vasc Anesth 20:477-483, 2006

19. Howie MB, Cheng DC, del Rio CL, et al: Desflurane versus propofol in OPCAB surgery: Is there a protective advantage? Anesthesiology 101:A256, 2004 (abstr)

20. DeMets DL, Pocock SJ, Julian DG: The agonising negative trend in monitoring of clinical trials. Lancet 354:1983-1988, 1999

21. Newcombe RG: Interval estimation for the difference between independent proportions: Comparison of eleven methods. Stat Med 17:873-890, 1998

22. Murry CE, Jennings RB, Reimer KA: Preconditioning with ischemia: A delay of lethal cell injury in ischemic myocardium. Circulation 74:1124-1136, 1986

23. Riess ML, Stowe DF, Waltier DC: Cardiac pharmacological preconditioning with volatile anesthetics: From bench to bedside? Am J Physiol Heart Circ Physiol 286:H1603-H1607, 2004

24. Conzen PF, Fischer S, Detter C, et al: Sevoflurane provides greater protection of the myocardium than propofol in patients undergoing off-pump coronary artery bypass surgery. Anesthesiology 99: 826-833, 2003

25. Bein B, Renner J, Caliebe D, et al: Sevoflurane but not propofol preserves myocardial function during minimally invasive direct coronary artery bypass surgery. Anesth Analg 100:610-616, 2005

26. De Hert SG, Van der Linden PJ, Stefanie Cromheecke S: Cardioprotective properties of sevoflurane in patients undergoing coronary surgery with cardiopulmonary bypass are related to the modalities of its administration. Anesthesiology 101:299-310, 2004

Volatile Agents for Cardiac Protection in Noncardiac Surgery: A Randomized Controlled Study

Alberto Zangrillo, MD,* Valentina Testa, MD,* Valeria Aldrovandi, MD,* Antonio Tuoro, MD,† Giuseppina Casiraghi, MD,* Francesca Cavenago, MD,* Melissa Messina, MD,* Elena Bignami, MD,* and Giovanni Landoni, MD*

Objective: **Volatile anesthetics reduce the risk of myocardial infarction and mortality in coronary artery surgery. Recently, the American College of Cardiology/American Heart Association Guidelines suggested the use of volatile anesthetic agents for the maintenance of general anesthesia during noncardiac surgery in patients at risk for perioperative myocardial ischemia, but no randomized experience to document the cardioprotective effects of these agents exists in this setting. Therefore, the authors performed a prospective, randomized, controlled trial to compare the effects of sevoflurane versus total intravenous anesthesia, in terms of postoperative cardiac troponin I release in patients undergoing noncardiac surgery.**

Design: **A randomized, controlled trial.**

Setting: **A teaching hospital.**

Participants: **Eighty-eight consecutive patients undergoing noncardiac surgery.**

Interventions: **Patients were allocated randomly to receive either volatile anesthetic (44 patients) as the main anesthetic agent or total intravenous anesthesia (TIVA) (44 patients).**

Measurements: **Postoperative cardiac troponin I release was measured as a marker of myocardial necrosis. Patients with detectable postoperative troponin I in the sevoflurane group (12/44, 27.3%) were similar to those in the propofol group (9/44, 20.5%; $p = 0.6$). There was no significant reduction of postoperative median peak cTnI release (0.16 ± 0.71 ng/mL in the sevoflurane group compared with the TIVA group, 0.03 ± 0.08 ng/mL; $p = 0.4$). Three patients died at the 1-year follow-up for noncardiac causes (2 in the TIVA group).**

Conclusions: **In the authors' experience, patients undergoing noncardiac surgery did not benefit from anesthesia based on halogenated anesthetics. Further studies are necessary to evaluate the cardioprotective effects of volatile agents in noncardiac surgery.**

KEY WORDS: halogenated anesthetics, volatile anesthetics, total intravenous anesthesia, noncardiac surgery, thoracic surgery, vascular surgery, cardiac troponin I, myocardial damage, anesthesia

CARDIAC DAMAGE IS one of the possible perioperative complications of cardiac and noncardiac surgery[1-4] and can lead to prolonged hospital stay as well as an increased perioperative morbidity and mortality rate. Cardiac troponin (cTn) is the most popular biomarker for myocardial damage, presenting with high myocardial tissue specificity and sensitivity, capable of detecting myocardial necrosis even at minimal amounts.[5] cTn predicts short- and long-term outcomes after cardiac[6] and noncardiac surgery.[7,8] The extent of cTn elevation is related directly with the magnitude of myocardial damage.[9]

Anesthetic strategies can directly affect the rate and entity of myocardial injury and subsequent patient outcomes. Volatile anesthetics, commonly used to induce and maintain hypnosis, analgesia, amnesia, and muscle relaxation, have shown the ability to improve postischemic recovery at the cellular level in isolated hearts and in animals, mainly through pharmacologic preconditioning.[10,11] There are 4 published articles suggesting a reduction in mortality in patients undergoing cardiac surgery and receiving volatile agents,[12-15] and a recent international consensus conference supported this point.[16,17] There is no published article suggesting a reduction in mortality in patients undergoing cardiac surgery with total intravenous anesthesia (TIVA).

Recent American College of Cardiology/American Heart Association Guidelines suggest that patients at high risk for myocardial ischemia undergoing noncardiac surgery who are hemodynamically stable could benefit from the use of volatile agents for the maintenance of anesthesia.[18] Whether such cardioprotective properties exist in noncardiac surgery settings is still unknown, and sufficient evidence is not available.[19] Recently, a meta-analysis of 79 randomized, controlled studies investigated whether the cardioprotective properties of desflurane and sevoflurane, widely shown in cardiosurgical patients, could possibly translate to a noncardiac surgery setting.[20] In contrast to the previously mentioned guidelines, the results of this meta-analysis could not support the hypothesis that the use of volatile anesthetics can reduce perioperative myocardial injury in noncardiac surgery.

Halogenated agents have cardioprotective properties and also mimic ischemic preconditioning, a powerful cardioprotec-

*From the Departments of *Anesthesia and Intensive Care and †Thoracic Surgery, Università Vita-Salute San Raffaele, Milan, Italy.*

Address reprint requests to Giovanni Landoni, MD, Department of Cardiothoracic Anesthesia and Intensive Care, Istituto Scientifico San Raffaele, Via Olgettina 60, Milan 20132, Italy. E-mail: landoni.giovanni@hsr.it

1053-0770/2506-0002$36.00/0

doi:10.1053/j.jvca.2011.06.016

tive phenomenon first described in 1986.[21,22] Myocardial cells exposed to brief sublethal episodes of ischemia show an adaptive response leading to an enhanced protection against subsequent lethal ischemia. A key question was whether the cardioprotective or the preconditioning effects of volatile anesthetics are clinically relevant, applicable, and associated with improved cardiac function, ultimately resulting in a better outcome in patients at high risk for myocardial infarction. Therefore, the authors performed a randomized trial to compare the cardioprotective effects of a volatile agent (sevoflurane) versus TIVA in patients undergoing noncardiac (thoracic and vascular) surgery. The hypothesis that volatile anesthetics would decrease perioperative myocardial damage as measured by cTnI release when compared with TIVA was tested.

MATERIALS AND METHODS

This prospective, randomized, single-blind, controlled study was performed according to Declaration of Helsinki principles. Ethical committee approval was obtained, and each patient signed a written informed consent. Consecutive patients with a Lee index ≥2 scheduled for elective lung surgery and major peripheral vascular surgery at a university hospital were assigned randomly to receive sevoflurane as the main anesthetic agent or a propofol-based TIVA. This article was written following the www.consort-statement.org checklist.

All subjects requiring one-lung ventilation for lung (using either thoracotomic or thoracoscopic approach) or peripheral revascularization surgery were eligible if they were over 18 years of age, signed the written informed consent, and planned for general anesthesia. Exclusion criteria were a previous unusual response to an anesthetic use of sulfonylurea, theophylline, or allopurinol.

Patients in the volatile anesthetics group received sevoflurane (Sevorane; Abbott, Queenborough, UK) 1% to 4% end-tidal concentration, corresponding to 0.5 to 2.0 end-tidal minimum alveolar concentration throughout the operation. Patients in the TIVA group received 4 to 6 mg/kg/h of propofol (Diprivan; Astra Zeneca, Brussel, Belgium) via target-controlled infusion.

Preoperative history, laboratory results, and an electrocardiogram were obtained, and an assessment of cardiac complications after noncardiac surgery risk was estimated through the Revised Cardiac Risk Index.[23] All preoperative medications were continued until the day of surgery except for aspirin, which was stopped 1 week before surgery; subcutaneous administration of heparin was started the evening before surgery. Preoperative β-blockers were continued postoperatively, if allowed by heart rate and blood pressure, to avoid withdrawal on the 1st postoperative day.

All patients were premedicated with diazepam (0.1 mg/kg intramuscularly). In patients undergoing thoracotomy, a thoracic epidural catheter was placed for postoperative pain control. Patients were monitored as follows: continuous electrocardiographic leads II and V_5 with ST-segment analysis, pulse oximetry, invasive radial artery blood pressure measurement, capnometry, and urine output. During anesthesia induction, each patient received an intravenous bolus of thiopental sodium (3-5 mg/kg), fentanyl (1-2 μg/kg), and atracurium besylate (0.5-0.6 mg/kg). Anesthesia was maintained with repeated doses of fentanyl (0.5 μg/kg), atracurium besylate, and with either volatile anesthetics or propofol as described previously. The authors recorded any of the following: use of inotropic or vasodilator drugs, intraoperative bleeding, blood product transfusion, intraoperative complication, and the need for postoperative intensive care. After surgery, muscle relaxation was reversed with atropine sulphate, 1 mg, and neostigmine, 2 mg; anesthesia was discontinued; and patients were extubated. Patients were transferred to the thoracic or vascular surgery unit when hemodynamically stable and conscious and with adequate pain control. Postoperative analgesic treatment consisted of tramadol + ketorolac or intravenous paracetamol and epidural administration of 4 to 6 mL/h of ropivacaine 0.2% (2 mg/mL) + sufentanyl (50 μg/mL) in patients with a thoracic epidural catheter.

The primary endpoint of the study was a dichotomous endpoint of detectable versus nondetectable postoperative cTnI. CTnI and an electrocardiogram were collected preoperatively and on the 1st and 2nd postoperative days. Data were collected by trained observers who did not participate in patient care and who were blinded to the anesthetic regimen used. Medical treatment and decision making in the ward were performed by physicians who were blinded to the anesthetic regimen used. Caregivers were interviewed daily for the occurrence of postoperative adverse events, and telephone interviews at 1 and 12 months after surgery were performed.

CTnI was used as a biomarker because it has myocardial tissue specificity and sensitivity and can detect microscopic zones of myocardial necrosis. An increased cTn measurement after surgery is an independent predictor of mortality.[24] Blood was collected in plastic tubes with a clot activator (Becton Dickinson Vacutainer Systems, Franklin Lakes, NJ) and was centrifuged (2,500*g* for 15 minutes) before analysis. CTnI was assayed with AIA 1800 (Tosoh, Tokyo, Japan) according to the manufacturer's instructions. The cTnI method is a 1-step enzyme immunoassay based on the sandwich principle. Sensitivity of the assay is 0.04 ng/mL.

On the basis of previous data investigating postoperative cTnI release,[25,26] the authors anticipated that the number of patients showing a detectable cTnI release would have been 40% and 10% in the TIVA and volatile anesthetics group, respectively. The authors calculated that a sample size of 38 patients per group would be needed. The authors planned to randomize 88 patients in order to account for possible protocol deviation. All patients were analyzed according to the intention-to-treat principle beginning immediately after randomization.

Randomization was conducted by a computer-generated list, and the details were contained in a set of sealed, opaque envelopes that were opened at the beginning of anesthesia. All study personnel, including those involved in cTnI measurement and participants, were blinded to treatment assignment for the duration of the study except the anesthesiologists who were not involved in data collection, data entry, or data analysis.

Data were stored electronically and analyzed by use of Epi Info 2002 software (CDC, Atlanta, GA) and SAS software, version 8 (SAS Institute, Cary, NC). All data analysis was performed according to a pre-established analysis plan. Dichotomous data were compared by using the 2-tailed chi-square test with the Yates correction or the Fisher exact test when appropriate. Continuous measures, including the primary outcome (cTnI), were compared by the Mann-Whitney *U* test. Two-sided significance tests were used throughout. Data are presented as median (25th and 75th percentiles) or as mean (± standard deviation) if not otherwise indicated.

RESULTS

In the study period, 88 consecutive qualifying and consenting patients were assigned randomly to receive either volatile anesthetics (44 patients) or TIVA (44 patients) (Fig 1). The baseline demographic and clinical characteristics of the 2 groups are summarized in Table 1; they showed no statistical difference and confirmed that the patients were at high risk (73% were American Society of Anesthesiologists ≥3, and all patients had a Lee score ≥2). Fentanyl administration did not differ between patients receiving volatile anesthetics (164 ± 57 μg) or TIVA (154 ± 68 μg; $p = 0.1$).

Twenty-one patients had detectable cTnI after surgery, with no differences between the volatile anesthetic group (12/44

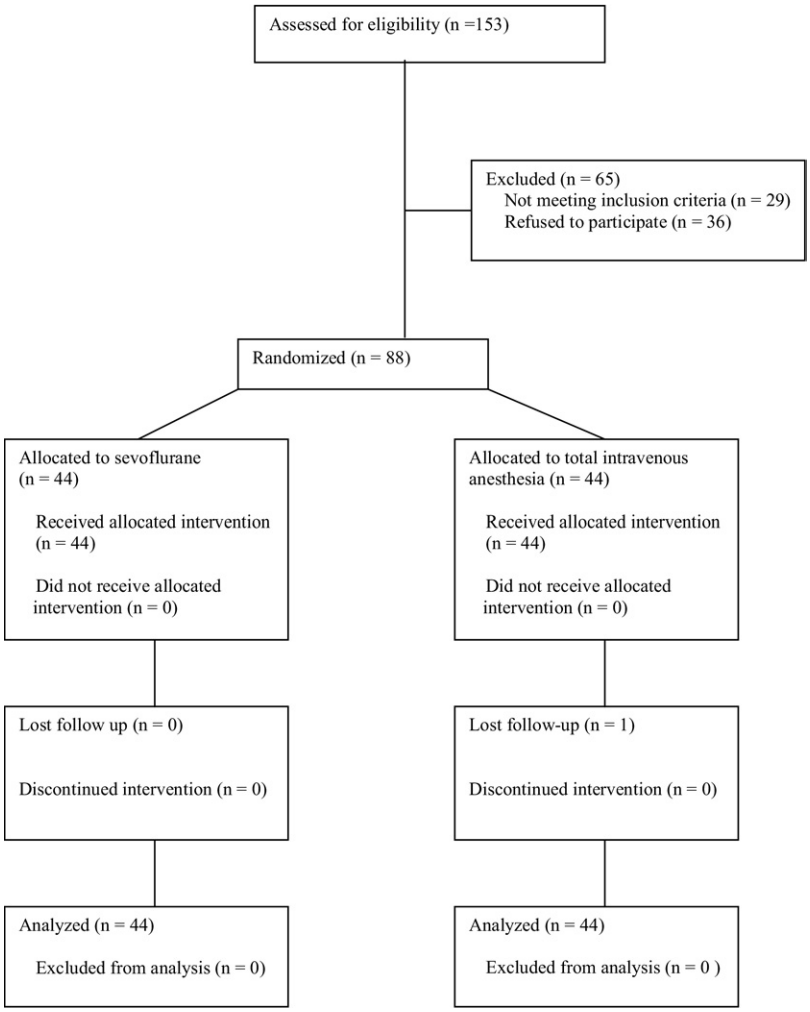

Fig 1. A flowchart of the randomization to receive either total intravenous anesthesia or volatile anesthesia for noncardiac surgery.

[27.3%]) and the TIVA group (9/44 [20.5%], $p = 0.6$). The peak postoperative cTnI release was 0.16 ± 0.71 ng/mL in the sevoflurane group versus 0.03 ± 0.08 ng/mL in patients receiving TIVA ($p = 0.4$).

No patient had perioperative ischemia or myocardial infarction. One patient (sevoflurane group) undergoing pneumonectomy had a severe intraoperative desaturation during lung removal, and 1 patient (sevoflurane group) had intraoperative arrhythmia (atrial fibrillation) treated with electrical cardioversion. Another patient (TIVA group) presented with intraoperative atrial fibrillation treated with amiodarone, and 1 patient (TIVA group) did not tolerate one-lung ventilation for severe desaturation. Two patients of the TIVA group had atrial fibrillation during the postoperative hospital stay. In-hospital mortality was 1 in 88; the patient (TIVA group), with a history of hypertension, asthma, metastatic uterine fibroma, and a high-grade lung neoplasia, died of respiratory failure because of lung cancer progression in the intensive care unit 8 days after surgery (Table 2).

Thirty-day complications occurred in 3 of 44 patients in the sevoflurane group (cancer progression, general weakness, and bronchial fistula) and in 6 of 43 patients in the TIVA group (electrical cardioversion for atrial fibrillation, cancer progression, pneumonia, general weakness, rehospitalization for wound dehiscence, and pulmonary embolism), with no significant differences between the 2 groups ($p = 0.2$). No additional events were recorded at the 30-day follow up (Table 3).

Three of 43 patients of the sevoflurane group presented with the following cardiac events at 1 year: cardiac arrhythmia, cardiac failure and infarction, and the need for percutaneous transluminal coronary angioplasty (PTCA); 1 of the 42 patients in the TIVA group had cardiac failure, with no significant differences between the 2 groups ($p = 0.3$). No differences between the 2 groups were noted in noncardiac postoperative complications at 1 year (5/43 patients in the sevoflurane group *v* 11/42 patients in the TIVA group, $p = 0.09$) and in 1-year mortality ($p = 0.5$) (Table 3).

DISCUSSION

This article suggests that patients undergoing noncardiac surgery (vascular and thoracic surgery) do not benefit from the cardioprotective properties of halogenated anesthetics in terms of reduced postoperative release of cTn. A recent meta-analysis showed that the use of desflurane and sevoflurane in cardiac

Table 1. Demographic, Clinical Characteristics, and Prerandomization Data of 88 Patients Who Received Sevoflurane (SEVO) or Propofol-Based TIVA for Noncardiac Surgery

Characteristics	SEVO (44 Patients)	TIVA (44 Patients)
Age, y	65 ± 11.8	64 ± 12.2
Weight, kg	72 ± 12.2	75 ± 13.9
Height, cm	168 ± 8.2	167 ± 9.1
Female sex, n (%)	9 (20.5)	14 (31.8)
Smoke, n (%)	13 (29.5)	9 (20.5)
American Society of Anesthesiologists, n (%)		
1	1 (2.3)	0
2	8 (18.2)	15 (34.1)
3	35 (79.5)	26 (59.1)
4	0	3 (6.8)
Lee Index, n (%)		
1	0	0
2	18 (40.9)	21 (47.7)
3	13 (29.5)	12 (27.3)
4	13 (29.5)	11 (25)
Hypertension, n (%)	21 (47.7)	18 (40.9)
Coronary artery disease, n (%)	13 (29.5)	19 (43.2)
Chronic obstructive pulmonary disease, n (%)	4 (9.1)	3 (6.8)
Chronic renal dysfunction, n (%)	2 (4.5)	4 (9.1)
Diabetes, n (%)	6 (13.6)	6 (13.6)
Preoperative Q-wave, n (%)	4 (9.1)	8 (18.2)
Cardiac arrhythmias (atrial fibrillation), n (%)	0	3 (6.8)
Medications		
β-Blockers, n (%)	8 (18.2)	11 (25)
Angiotensin-converting enzyme, n (%)	11 (25)	11 (25)
Antiarrhythmics, n (%)	1 (2.3)	6 (13.6)
Diuretics, n (%)	5 (11.4)	12 (27.3)
Calcium antagonists, n (%)	8 (18.2)	9 (20.5)
Angiotensin II antagonists, n (%)	8 (18.2)	10 (22.7)
Nitrates, n (%)	5 (11.4)	9 (20.5)
Insulin, n (%)	5 (11.4)	5 (11.4)
Statins, n (%)	10 (22.7)	10 (22.7)
Antiplatelets, n (%)	5 (11.4)	8 (18.2)
Thoracic surgery, n (%)	22 (50)	22 (50)
Vascular surgery, n (%)	22 (50)	22 (50)
Thoracic epidural catheter, n (%)	18 (40.9)	18 (40.9)

surgery reduces postoperative mortality and the incidence of myocardial infarction (MI), with a significantly lower need for inotropic support, time on mechanical ventilation, intensive care unit stay, and overall hospital stay.[12] In this meta-analysis, 15 articles analyzed postoperative cTn release, and all of them showed a reduction in the release of cTn in patients receiving volatile agents when compared with TIVA group patients. Overall, the reduction was quantified in a weighted mean difference of 2.35 ng/dL (−3.09 to −1.60), a p for effect value <0.001, a p for heterogeneity value <0.001, and I^2 of 94.1% with 1,463 included patients. Three other recent studies[13-15] performed in a cardiac surgical setting confirmed these data.

Few randomized studies were performed in noncoronary artery bypass graft surgery. In aortic valve surgery, the use of volatile agents led to a better recovery of cardiac function after cardiopulmonary bypass and a lower postoperative cTnI release when compared with a TIVA regimen.[27] However, such effects were not observed in mitral valve surgery.[28] Only 1 study was performed in a nonsurgical setting.[29] Investigating the cardioprotective properties of volatile anesthetics in the setting of stenting procedures, the authors randomly assigned 16 patients to breathe sevoflurane (expired end-tidal concentration 1%) and 14 patients to breathe a placebo oxygen/air mix before stenting procedures. At the end of 20 minutes, the patients entered the washout period spontaneously breathing air. Ten minutes after the washout period, patients were transferred to the cardiology laboratory for percutaneous coronary intervention with stent implantation. Sixteen patients had detectable cTnI after stenting procedures, with no differences between groups, 10 (62%) in the sevoflurane group versus 6 (43%) in the placebo group ($p = 0.3$). The authors concluded that pharmacologic preconditioning with low-dose sevoflurane before interventional cardiology procedures does not lead to an advantage in terms of myocardial injury when compared with placebo administration. Even if the recent American College of Cardiology/American Heart Association Guidelines recommended the use of volatile anesthetic agents during noncardiac surgery for the maintenance of general anesthesia in patients at risk for MI (class IIa, level of evidence B), no randomized experience to document the cardioprotective properties of volatile agents in noncardiac surgery existed.

A recent meta-analysis[20] included 79 studies involving 6,219 patients (2,768 received TIVA, and 3,451 received desflurane or sevoflurane in their anesthesia plan) undergoing noncardiac surgery. Inclusion criteria were random allocation to treatment, comparison of a TIVA regimen versus an anesthesia plan including desflurane or sevoflurane, and performed on adult noncardiosurgical patients. No author reported any postopera-

Table 2. Postrandomization Data of 88 Patients Who Received Sevoflurane (SEVO) or Propofol-Based TIVA for Noncardiac Surgery

Characteristics	SEVO (44 Patients)	TIVA (44 Patients)	p Value
Opiates (fentanyl), μg	164 ± 57	154 ± 68	0.5
Inotropes, n (%)	0	2 (4.5)	0.3
Vasodilators, n (%)	3 (6.8)	8 (18.2)	0.2
Bleeding, mL	204 ± 314	179 ± 245	0.7
Use of blood products, n (%)	3 (6.8)	6 (13.6)	0.2
Intraoperative complications, n (%)	2 (4.5)	2 (4.5)	0.9
Intraoperative cardiac complications (atrial fibrillation), n (%)	1 (2.3)	1 (2.3)	0.9
Postoperative complications, n (%)	0	3 (6.8)	0.1
Q-wave myocardial infarction, n (%)	0	0	—
Postoperative cardiocirculatory failure, n (%)	0	0	—
Transfer to the intensive care unit, n (%)	1 (2.3)	4 (9.1)	0.2
Intensive care unit complications, n (%)	0	0	—

Table 3. Postrandomization Data of 88 Patients Who Received Sevoflurane (SEVO) or Propofol-Based TIVA for Noncardiac Surgery

Characteristics	SEVO (44 Patients)	TIVA (44 Patients)	*p* Value
Cardiac events at 30 days, n (%)	0	0	—
Other complications at 30 days, n (%)	3 (6.8)	6 (13.6)	0.2
Cardiac death at 30 days, n (%)	0	0	—
Noncardiac death at 30 days, n (%)	0	1 (2.3)	0.5
Cardiac events at 1 year, n (%)	3 (6.8)	1 (2.3)	0.3
Other complications at 1 year, n (%)	5 (11.4)	11 (25)	0.2
	Aortobifemoral bypass	Cardioversion for atrial fibrillation	
	Neoplasia	Lymphoma	
	Femoral popliteal bypass occlusion and reintervention	Cerebral metastases	
		Liver disease and esophageal variceal rupture	
	Femoral popliteal bypass occlusion and reintervention	Cancer progression	
	Ictus cerebri	Neoplasia	
		Cryoablation for suprarenal tumor	
		Hypertension	
		Spontaneous pneumothorax	
		Cerebral and pulmonary metastases	
		Lymphoma	
Cardiac death at 1 year, n (%)	0	0	—
Noncardiac death at 1 year, n (%)	1 (2.3)	2 (4.5)	0.5
	Neoplasia	Neoplasia	
		Neoplasia	

tive MI or death among the study population or any significant adverse cardiac event. Up to the present time, none of the randomized studies comparing halogenated with intravenous anesthetics has ever addressed major outcomes such as MI or mortality or cardiac outcomes such as cTn release.

Recently, a retrospective analysis[30] showed no difference in postoperative cardiac events and the postoperative cTn peak level between patients receiving a volatile anesthetic versus a nonvolatile anesthetic regimen. In 2009, De Conno et al[31] randomized 54 patients undergoing elective thoracic surgery to receive either total intravenous anesthesia with propofol or inhalation anesthesia with sevoflurane. In both groups, the induction of anesthesia was performed with the intravenous anesthetic propofol, whereas the maintenance of anesthesia was performed with either propofol or sevoflurane according to randomization. In the propofol group, the authors described a significant increase of inflammatory mediators, except interleukin-1, compared with the sevoflurane group. The overall number of adverse events (ie, prolonged antibiotics, pneumonia, atelectasis, fistula, reintubation, surgical revision, and sepsis) in the propofol group was significantly higher than in the sevoflurane group (40 *v* 18). Moreover, patients in the propofol group had a significantly longer intensive care unit stay compared with patients in the sevoflurane group (1.52 ± 2.33 *v* 0.87 ± 0.43 days). In this study, volatile agents were shown to have an important organ-protective effect. Their use was associated with a reduction of the inflammatory response after one-lung ventilation surgery, leading to a significantly better clinical outcome, which was defined as a reduction of adverse events. In a recent randomized article, Van der Linden et al[32] reported 4 major postoperative cardiovascular complications, 3 deaths in the total intravenous group (20 patients), and no event in the sevoflurane group (20 patients), but they did not report postoperative cardiac biomarker levels in a cohort of patients undergoing peripheral arterial bypass grafting.

Limitations

The patients were presumably "at risk" for intraoperative ischemic events although preoperative documentation (eg, a history of angina, nuclear or exercise stress test, dobutamine stress echocardiography, and cardiac catheterization) was not collected. Notably, no patient had perioperative myocardial infarction or ischemia, and it could be argued that no cardioprotective effect was possible if no cardiac ischemia occurred. Furthermore, the study focused on a surrogate endpoint (a cardiac biomarker instead of a clinically relevant outcome). The authors also acknowledged that these results came from a relatively small, heterogenous (thoracic and vascular surgery with or without an epidural catheter) sample of patients and that further studies are warranted in this setting.

The sample size calculation probably was based on a too optimistic expected treatment effect, and, consequently, the study was underpowered to identify differences in cTn release, but the results can be used as pilot data to determine the sample size of a larger study; if the authors identify a population with 20% of patients having a detectable postoperative cTn release and consider that a decrease from 20% to 15% with the use of a different anesthetic plan would be clinically relevant, they would expect to plan a randomized study with approximately 950 patients per group. On the other hand, the possibility to perform small, methodologically correct, randomized studies reporting clinically relevant outcomes with the intention-to-treat principle and to pool the results using a meta-analytic process should be considered.[33]

CONCLUSIONS

The present data cannot support the recommendations of the recent guidelines that suggested the use of volatile agents in

patients at risk for coronary artery disease undergoing noncardiac surgery. Further studies are necessary to evaluate the role of cardioprotective effects of volatile anesthetics, especially in patients undergoing high-risk noncardiac surgery.

ACKNOWLEDGMENTS

The authors thank Isotta Virzo, RN, Giulio Cozzuto, RN, Giuseppe Giardina, RN, and P. Zuppelli, RA, for their invaluable support.

REFERENCES

1. Edwards FH, Peterson ED, Coombs LP, et al: Prediction of operative mortality after valve replacement surgery. J Am Coll Cardiol 37:885-892, 2001

2. Akins CW, Miller DC, Turina MI, et al: Guidelines for reporting mortality and morbidity after cardiac valve interventions. Ann Thorac Surg 85:1490-1495, 2008

3. Devereaux PJ, Goldman L, Cook DJ, et al: Perioperative cardiac events in patients undergoing noncardiac surgery: A review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. CMAJ 173:627-634, 2005

4. Kikura M, Oikawa F, Yamamoto K, et al: Myocardial infarction and cerebrovascular accident following non-cardiac surgery: Differences in postoperative temporal distribution and risk factors. J Thromb Haemost 6:742-748, 2008

5. Thygesen K, Alpert JS, White HD: Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. J Am Coll Cardiol 50:2173-2195, 2007

6. Croal BL, Hillis GS, Gibson PH, et al: Relationship between postoperative cardiac troponin I levels and outcome of cardiac surgery. Circulation 114:1468-1475, 2006

7. Ali ZA, Callaghan CJ, Ali AA, et al: Perioperative myocardial injury after elective open abdominal aortic aneurysm repair predicts outcome. Eur J Vasc Endovasc Surg 35:413-419, 2008

8. Kim LJ, Martinez EA, Faraday N, et al: Cardiac troponin I predicts short-term mortality in vascular surgery patients. Circulation 106:2366-2371, 2002

9. Selvanayagam JB, Petersen SE, Francis JM, et al: Effects of off-pump versus on-pump coronary surgery on reversible and irreversible myocardial injury: A randomized trial using cardiovascular magnetic resonance imaging and biochemical markers. Circulation 109: 345-350, 2004

10. Riess ML, Stowe DF, Waltier DC: Cardiac pharmacological preconditioning with volatile anesthetics: From bench to bedside? Am J Physiol Heart Circ Physiol 286:H1603-H1607, 2004

11. De Hert SG, Turani F, Mathur S, et al: Cardioprotection with volatile anesthetics: Mechanisms and clinical implications. Anesth Analg 100:1584-1593, 2005

12. Landoni G, Biondi-Zoccai GL, Zangrillo A, et al: Desflurane and sevoflurane in cardiac surgery: A meta-analysis of randomized clinical trials. J Cardiothorac Vasc Anesth 21:502-511, 2007

13. Bignami E, Biondi-Zoccai G, Landoni G, et al: Volatile anesthetics reduce mortality in cardiac surgery. J Cardiothorac Vasc Anesth 23:594-599, 2009

14. Jakobsen CJ, Berg H, Hindsholm KB, et al: The influence of propofol versus sevoflurane anesthesia on outcome in 10,535 cardiac surgical procedures. J Cardiothorac Vasc Anesth 21:664-671, 2007

15. De Hert S, Vlasselaers D, Barbé R, et al: A comparison of volatile and non volatile agents for cardioprotection during on-pump coronary surgery. Anaesthesia 64:953-960, 2009

16. Landoni G, Augoustides JG, Guarracino F, et al: Mortality reduction in cardiac anesthesia and intensive care: Results of the first International Consensus Conference. Acta Anaesthesiol Scand 55:259-266, 2011

17. Landoni G, Augoustides JG, Guarracino F, et al: Mortality reduction in cardiac anesthesia and intensive care: results of the first International Consensus Conference. hSR proceedings in intensive care and cardiovascular anesthesia 3:9-19, 2011

18. Fleisher LA, Beckman JA, Brown KA, et al: 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. J Am Coll Cardiol 50:1707-1732, 2007

19. Landoni G, Fochi O, Tritapepe L, et al: Cardiac protection by volatile anesthetics. A review. Minerva Anestesiol 75:269-273, 2009

20. Landoni G, Fochi O, Bignami E, et al: Cardiac protection by volatile anesthetics in non-cardiac surgery? A meta-analysis of randomized controlled studies on clinically relevant endpoints. HSR Proc Intensive Care Cardiovasc Anesth 4:28-33, 2009

21. Murry CE, Jennings RB, Reimer KA: Preconditioning with ischemia: A delay of lethal cell injury in ischemic myocardium. Circulation 74:1124-1136, 1986

22. Torri G: Inhalation anesthetics: A review. Minerva Anestesiol 76:215-228, 2010

23. Lee TH, Marcantonio ER, Mangione CM, et al: Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 100:1043-1049, 1999

24. Levy M, Heels-Ansdell D, Hiralal R, et al: Prognostic value of troponin and creatine kinase muscle and brain isoenzyme measurement after noncardiac surgery: A systematic review and meta-analysis. Anesthesiology 114:796-806, 2011

25. Tambyraja AL, Dawson ARW, Murie JA, et al: Cardiac troponin I predicts outcome after ruptured abdominal aortic aneurysm repair. Br J Surg 92:824-827, 2005

26. Ali ZA, Callaghan CJ, Ali AA, et al: Perioperative myocardial injury after elective open abdominal aortic aneurysm repair predicts outcome. Eur J Vasc Endovasc Surg 35:413-419, 2008

27. Cromheecke S, Pepermans V, Hendrickx E, et al: Cardioprotective properties of sevoflurane in patients undergoing aortic valve replacement with cardiopulmonary bypass. Anesth Analg 103:289-296, 2006

28. Landoni G, Calabrò MG, Marchetti C, et al: Desflurane versus propofol in patients undergoing mitral valve surgery. J Cardiothorac Vasc Anesth 21:672-677, 2007

29. Landoni G, Zangrillo A, Fochi O, et al: Cardiac protection with volatile anesthetics in stenting procedures. J Cardiothorac Vasc Anesth 22:543-547, 2008

30. De Hert SG, Longrois D, Yang H, et al: Does the use of a volatile anesthetic regimen attenuate the incidence of cardiac events after vascular surgery? Acta Anaesthesiol Belg 59:19-25, 2008

31. De Conno E, Steurer MP, Wittlinger M, et al: Anesthetic induced improvement of the inflammatory responses to one lung ventilation. Anesthesiology 110:1316-1326, 2009

32. Van der Linden PJ, Dierick A, Wilmin S, et al: A randomized controlled trial comparing an intraoperative goal-directed strategy with routine clinical practice in patients undergoing peripheral arterial surgery. Eur J Anaesthesiol 27:788-793, 2010

33. Biondi-Zoccai G, Landoni G, Modena MG: A journey into clinical evidence: From case reports to mixed treatment comparisons. HSR Proc Intensive Care Cardiovasc Anesth 3:93-96, 2011

Acta Anaesthesiol Scand 2012; **56:** 482–490
Printed in Singapore. All rights reserved

ACTA ANAESTHESIOLOGICA SCANDINAVICA
doi: 10.1111/j.1399-6576.2011.02570.x

Sevoflurane vs. propofol in patients with coronary disease undergoing mitral surgery: a randomised study

E. Bignami[1], G. Landoni[1,2], C. Gerli[1], V. Testa[1], A. Mizzi[1], G. Fano[1], M. Nuzzi[1], A. Franco[1] and A. Zangrillo[1]
[1]*Department of Anesthesia and Intensive Care, Università Vita-Salute San Raffaele, Milan, Italy and* [2]*Outcomes Research Consortium, Cleveland, Ohio, USA*

Background: Myocardial ischemic damage is reduced by volatile anaesthetics in patients undergoing low-risk coronary artery bypass graft surgery; few and discordant results exist in other settings. We therefore performed a randomised controlled trial (sevoflurane vs. propofol) to compare cardiac troponin release in patients with coronary disease undergoing mitral surgery.
Methods: Patients with coronary artery disease undergoing mitral surgery were randomly allocated to receive either sevoflurane (50 patients) or propofol (50 patients) as main hypnotic. The primary endpoint of the study was peak post-operative cardiac troponin release defined as the maximum value among the post-operative values measured at intensive care unit arrival, 4 h later, on the first and second post-operative day.
Results: There was no significant difference in post-operative peak troponin release, the median (25th–75th percentiles) values being 14.9 (10.1–22.1) ng/ml and 14.5 (8.8–17.6) ng/ml in the sevoflurane and propofol groups, respectively ($P = 0.4$). Fentanyl administration was different between the two groups: 1347 ± 447 μg in patients receiving sevoflurane and 1670 ± 469 μg in those receiving propofol, $P = 0.002$. The 1-year follow-up identified two patients who died in the propofol group (one myocardial infarction and one low cardiac output syndrome) and one in the sevoflurane group (myocardial infarction).
Conclusion: In this study, patients with coronary artery disease undergoing mitral surgery did not benefit from the cardioprotective properties of halogenated anaesthetics. Sevoflurane anaesthesia was not associated to lower cardiac troponin release when compared with propofol anaesthesia.

Accepted for publication 7 September 2011

Cardiac damage following cardiac surgery could lead to post-operative depression of myocardial performance with a consequent prolonged hospital stay and an increased perioperative morbidity and mortality rate. Myocardial injury and subsequent patient outcomes can be modified by anaesthetic strategies. Volatile anaesthetics, commonly used to induce and maintain hypnosis, analgesia, amnesia, and muscle relaxation, improve post-ischemic recovery at the cellular level in isolated hearts, in animals, and in clinical studies.[1–3]

Meta-analyses[4–6] of randomised studies had discordant results when addressing clinically relevant outcomes after cardiac surgery performed with or without volatile agents.

Cardiac troponin I (cTnI) is the most popular biomarker for myocardial damage, with nearly total myocardial tissue specificity and extreme sensitivity, reflecting a very small amount of myocardial necrosis, and it predicts short- and long-term outcomes after cardiac and non-cardiac surgery. The magnitude of myocardial injury directly correlates with the extent of cTnI elevation.[7]

Even if an increasing number of reviews[8,9] and clinical studies showed the cardioprotective effects of volatile anaesthetics in patients undergoing coronary artery bypass graft (CABG) surgery with cardiopulmonary bypass (CPB)[10–13] or on the beating heart,[14–16] few and discordant results exist in valvular surgery.[17,18]

Recent guidelines suggested the use of volatile agents in haemodynamically stable patients undergoing non-cardiac surgery who are at risk for perioperative myocardial infarction,[19] even if no data exist in this setting[20] except an experience in stenting procedures.[21]

Jakobsen et al.[22] retrospectively studied 10,535 patients undergoing single (non-combined) cardiac

surgical procedures and showed that in haemodynamically unstable patients (undergoing urgent CABG), there was a reduction in mortality with total intravenous anaesthesia (TIVA) (8.19% in the propofol group vs. 16.23% in the sevoflurane group, $P = 0.031$).

No randomised trial exists on the effects of volatile agents in patient with coronary artery disease undergoing mitral surgery. We therefore performed a randomised controlled study (sevoflurane vs. propofol) to investigate whether the cardioprotective properties of volatile agents are confirmed in these patients and could contribute to reduce peak cardiac troponin release defined as the maximum value among the post-operative values measured at intensive care unit (ICU) arrival, 4 h later, on the first and second post-operative day.

Methods

This prospective, randomised, single-blind, controlled study was carried out according to Declaration of Helsinki principles. The ethical committee approved the study, and written informed consent was obtained from each patient.

Consecutive patients with coronary artery disease, scheduled for elective mitral valve surgery at a university hospital, were randomly assigned to receive sevoflurane as the main anaesthetic agent or a propofol-based TIVA. This paper is written following the http://www.consort-statement.org check list.

All subjects with coronary artery disease planned for mitral valve surgery under general anaesthesia were eligible if they were over 18 years of age, signed the written informed consent, and had at least one coronary vessel with a stenosis > 50% at the coronary angiogram. Patients were excluded in the case of previous unusual response to an anaesthetic, use of sulfonylurea, theophylline, or allopurinol, elevated pre-operative cTnI.

During anaesthesia induction, each patient received an intravenous bolus of propofol (1–2 mg/kg), fentanyl (5–10 μg/kg), and rocuronium (0.1 mg/kg). Patient monitoring included invasive radial artery blood pressure measurement, continuous electrocardiographic leads II, and V5 with ST segment monitoring, pulse oximetry, central venous pressure, capnometry, and urine output.

Patients in the volatile anaesthetics group received sevoflurane (Sevorane, Abbott, Queenborough, UK) 0.5 to 2.0 end-tidal minimum alveolar concentration, equal to 1% to 4%, before CPB starting immediately after intubation and again after CPB; this anaesthetic has known beneficial effects on post-ischemic mechanical and coronary function.[23,24]

Patients in the TIVA group received 2–3 $mg \times kg^{-1} \times h^{-1}$ propofol (Diprivan, Astra Zeneca, Brussels, Belgium) via target-controlled infusion since this drug represents the standard hypnotic drug during CPB in most cardiac anaesthesia units but has no known pharmacologic pre-conditioning effects.

During CBP, all patients received propofol on top of an opioid (fentanyl)-based anaesthesia. All patients received an intra-operative infusion of tranexamic acid; no aprotinin was administered. All patients underwent mitral valve surgery using a median sternotomy approach.

Pre-operative history, laboratory results, and electrocardiogram were obtained. Demographics and clinical characteristics were collected as described in Table 1 together with transoesophageal echocardiography data (collected at least 1 day before surgery).

All pre-operative medications were continued until the day of surgery except aspirin (stopped 1 week before surgery) and angiotensin-converting enzyme inhibitors (withdrawn on hospital admission, generally 1 day before surgery). Pre-operative beta blockers were continued post-operatively if permitted by heart rate, blood pressure, and cardiac index evaluation. No other drugs were continued routinely or given for cardiac protection. All patients were pre-medicated with diazepam, 0.1 mg/kg orally, morphine, 0.1 mg/kg, and scopolamine 0.25 mg intramuscularly, and received standard monitoring.

CPB was conducted at moderate hypothermia (32–34°C). Myocardial protection during aortic cross-clamping was obtained by antegrade and/or retrograde cold blood cardioplegia. Activated clotting time was maintained greater than 480 s for CPB; the effect of heparin (starting dose 300 U/kg) was reversed with protamine sulphate in a 1 : 1 ratio. If the target mean arterial pressure of 65 mmHg was not achieved with volume loading to a central venous pressure of 10 cm H_2O after weaning from CPB, an infusion of dopamine (initial dose 5 μg/kg/min) was started.

Following surgery, patients were transferred to the ICU, sedated with propofol for 4 h and weaned from the ventilator as soon as they were haemodynamically stable with no major bleeding, and with normothermia, an adequate level of consciousness, and a proper pain control had been achieved.

Table 1

Baseline demographic and clinical characteristics of 100 patients receiving either volatile anaesthetics (50 patients) or total intravenous anaesthesia (TIVA) (50 patients) to prevent perioperative myocardial damage.

Variables	Volatile anaesthetics (n = 50) (%)	TIVA (n = 50) (%)
Age (in years)	67 ± 8.1	66 ± 8.2
Female sex	13 (26)	11 (22)
Height	167 ± 8.7	168 ± 8.9
Weight (in kg)	69 ± 11.3	69 ± 12.6
Body mass index (in kg/m^2)	24.9 ± 4.1	24.2 ± 3.4
New York Heart Association		
II	29 (58)	35 (70)
III	21 (42)	14 (28)
IV	0 (0)	1 (2)
Euroscore	7.5 ± 2.9	7.1 ± 2.8
Euroscore predicted mortality, %	7.1 (4.5–14.0)	6.9 (3.7–12.3)
Chronic Obstructive Pulmonary disease	2 (4)	3 (6)
Diabetes	5 (10)	1 (2)
Hypertension	28 (56)	29 (58)
Severe vasculopathy	12 (24)	6 (12)
Anamnestic stroke	3 (6)	0 (0)
Previous cardiac surgery	4 (8)	5 (10)
Previous acute myocardial infarction	11 (22)	16 (32)
Chronic atrial fibrillation	9 (18)	6 (12)
Paroxysmal atrial fibrillation	5 (10)	8 (16)
Medicaments		
Angiotensin-converting enzyme inhibitors	28 (56)	26 (52)
Beta blockers	20 (40)	19 (38)
Calcium antagonists	6 (12)	6 (12)
Diuretics	28 (56)	27 (54)
Statins	9 (18)	3 (6)
Digoxin	3 (6)	4 (8)
Nitroglycerin	8 (16)	4 (8)
Transoesophageal echocardiography data		
Ejection Fraction	54.4 ± 12.5	55.9 ± 13.3
End-diastolic diameter (in mm)	56.5 ± 8.8	57.0 ± 8.7
End-diastolic volume (in ml)	125.9 ± 42.0	132.1 ± 56.2
End-systolic diameter (in mm)	36.2 ± 6.2	35.4 ± 8.8
End-systolic volume (in ml)	52.2 ± 30	48.2 ± 28.5
Pulmonary artery pressure (in mmHg)	46.7 ± 17.5	40.5 ± 10.1
Intra-ventricular septum (in mm)	12.4 ± 1.7	12 ± 1.9
Mitral insufficiency	50 (50)	50 (50)
Mitral stenosis	5 (10)	1 (2)

Weaning from catecholamine infusion was guided by standard haemodynamic criteria. Post-operative pain relief was provided to all patients by boluses of intravenous morphine. Blood pressure (systolic, mean, and diastolic), heart rate, and central venous pressure were recorded at seven time points: before induction of anaesthesia, before and after CPB, at ICU arrival, and at 4, 8, and 12 h later. Neurologic events were classified into type I (focal injury, stupor, or coma at discharge) and type II (deterioration in intellectual function, memory deficit, or seizures).

Myocardial infarction was defined as suggested by the recent consensus conference for the universal definition of myocardial infarction:[25] biomarker values more than five times the 99th percentile of the normal reference range during the first 72 h following surgery, when associated with the appearance of new pathological Q wave or new left bundle branch block, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium. New Q waves were defined as the appearance of a Q wave ≥40 ms in at least two adjacent leads or as the loss of R wave amplitude in pre-cordial leads.

Criteria for hospital discharge were haemodynamic and cardiac rhythm stability, the presence of clean and dry incisions, an afebrile condition, normal bowel movement, and independent ambulation and feeding. Follow-up was performed at 30 days and at 6 months after the operation.

The primary endpoint of the study was a reduction in post-operative cTnI release peak defined as the maximum value among the post-operative values measured at ICU arrival, 4 h later, on the first and second post-operative day. Data were collected by trained observers who did not participate in patient care and who were blinded to the anaesthetic regimen used. Medical treatment and decision-making in the ICU and in the ward were performed by physicians who were blinded to the anaesthetic regimen used. Caregivers were interviewed daily for the occurrence of post-operative adverse events and a telephone interview at 1 and 12 months after surgery was carried out.

cTnI, which has nearly absolute myocardial tissue specificity, as well as high sensitivity, thereby reflecting even microscopic zones of myocardial necrosis, was used as a biomarker. Blood was collected in plastic tubes with clot activator (Becton Dickinson Vacutainer Systems, Franklin Lakes, NJ, USA) and was centrifuged (2500 g for 15 min) before analysis. cTnI was assayed with AIA 1800 (Tosoh Corporation, Tokyo, Japan) according to the manufacturer's instructions. This method is a one-step enzyme immunoassay based on the sandwich principle. Sensitivity of the assay is 0.04 ng/ml.

Statistical analysis

Sample size calculation was based on a two-sided alpha error of 0.05 and 80% power. On the basis of a previous report[17] investigating cTnI release after mitral valve surgery, we anticipated a mean post-operative peak cTnI release of 30 ± 10 ng/ml in the TIVA group and assumed a 6 ng/ml reduction in peak cTnI concentration after treatment with volatile anaesthetics to be clinically relevant. We calculated that we would need a sample size of 45 patients per group. However, we planned to randomly select 100 patients in order to take into account possible protocol deviations. All 100 patients were analysed according to the intention to treat principle beginning immediately after randomisation. Our sample size calculation followed the suggestions of the consensus conference:[25] the analysis of the actual distribution of myocardial damage observed (peak value of a biomarker) is more appropriate than the analysis of the simple presence or absence of events.

The details of the randomisation, created by a computer-generated list, were contained in a set of sealed, opaque envelopes that were opened at the beginning of anaesthesia. All study personnel (including those involved in cTnI measurement) and participants were blinded to treatment assignment for the duration of the study, except the anaesthesiologists who were not involved in data collection, data entry, or data analysis. Data were stored electronically and analysed with Epi Info 2002 software (Centre for Disease Control, Atlanta, GA, USA) and SAS software, version 8 (SAS Institute, Cary, NC, USA). All data analyses were carried out according to a pre-established analysis plan. Dichotomous data were compared by using two-tailed χ^2 test with the Yates correction or Fisher's exact test when appropriate. Continuous measures, including the primary outcome (cTnI), were compared by Mann–Whitney *U*-test. Two-sided significance tests were used throughout. Data are presented as median (25th–75th percentiles) or as mean ± standard deviation, if not otherwise indicated.

Results

Between June 2006 and August 2008, 100 consecutive consenting patients were randomly assigned to receive either sevoflurane (50 patients) or TIVA (50 patients) (Fig. 1). The baseline demographic and clinical characteristics of the two groups are

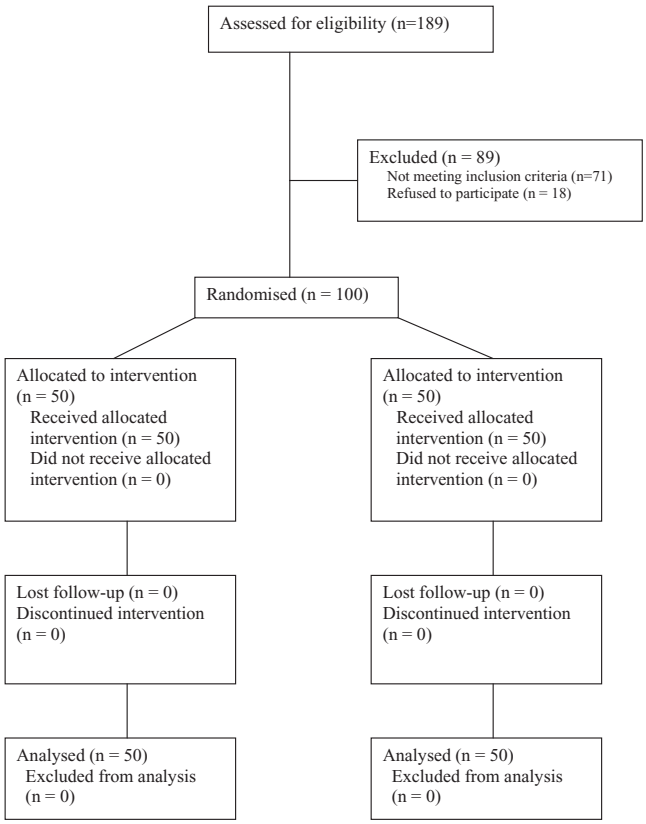

Fig. 1. Flow diagram.

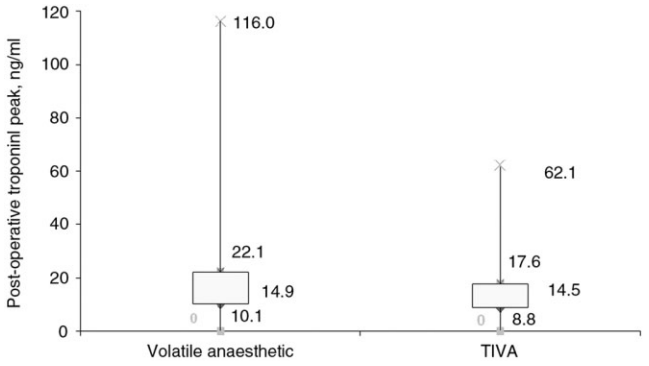

Fig. 2. Median (25th–75th percentiles) post-operative troponin I peak (maximum value between the post-operative values measured at ICU arrival, 4 h later, on the first and second post-operative day) in patients receiving sevoflurane and in those receiving TIVA.

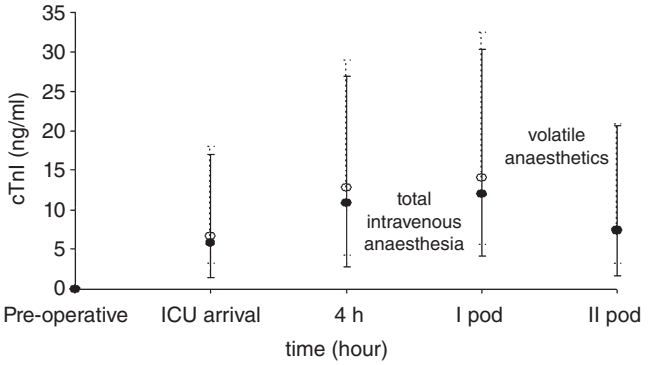

Fig. 3. Median (25th–75th percentiles) of troponin release at ICU arrival, 4 h later and on first and second post-operative day in patients receiving either volatile anaesthetics or TIVA. Pod, post-operative day.

summarised in Table 1. Heart rate, central venous pressure, blood pressure (systolic, mean, and diastolic), temperature, and arterial blood results were similar in the two groups in all the seven time points (data not shown). Two included patients scheduled for mitral surgery never had this surgery performed. This change was due to a perioperative decision to avoid mitral surgery in these patients. Data of these two patients were analysed according to the intention to treat principle.

All patients had detectable cTnI after mitral valve surgery, with no significant reduction of myocardial damage in patients receiving sevoflurane as documented by a post-operative median (interquartile) peak cTnI release of 14.9 (10.1–22.1) ng/ml compared with that of patients receiving propofol, 14.5 (8.8–17.6) ng/dl ($P = 0.4$) (Fig. 2). Figure 3 shows cTnI levels at different points in time. Troponin release at ICU arrival, 4 h later, and on the first and the second post-operative day showed no statistically significant differences at any time point (Fig. 3).

Post-randomisation data and clinical outcomes are reported in Table 2 and show no statistically significant difference between groups with the exception of fentanyl administration that was slightly less (1347 + 447 μg) in patients receiving sevoflurane anaesthetics when compared with those receiving propofol (1670 + 469 μg), $P = 0.002$.

Three patients (3%) died, two in the propofol group and one in the sevoflurane group. Causes of death were represented by acute myocardial infarction (one in each group) and refractory low cardiac output syndrome (one patient in propofol group). These patients died in the hospital. No further death was observed at the 1-year follow-up.

Discussion

This study represents the first randomised study (sevoflurane vs. propofol) in patients with coronary disease undergoing mitral surgery. No cardioprotective effect of volatile anaesthetics was found in this population in terms of post-operative peak cTnI release.

The mechanisms underlying the benefits of halogenated anaesthetics are not completely clear. These effects could be, in part, explained by a mechanism similar to ischemic pre-conditioning but not requiring ischemia.[26] Volatile agents seem to be able to trigger an acute cardioprotective memory effect called anaesthetic or pharmacologic preconditioning. These drugs seem to have also a post-conditioning effect that may contribute to protection when administered after the onset of ischemia.

An increasing number of studies showed protective effects by halogenated anaesthetics in low-risk patients undergoing CABG with CPB[10–13] or on the beating heart,[14–16] and a meta-analysis of 22 included trials that randomised 1922 patients (904 to TIVA and 1018 receiving desflurane or sevoflurane in their anaesthesia plan) suggested, for the first time, a reduction in the risk of myocardial infarction [24/979 (2.4%) in the volatile anaesthetics group vs. 45/874 (5.1%) in the control arm, $P = 0.008$] and of all-cause mortality [4/977 (0.4%) vs. 14/872 (1.6%), $P = 0.002$], confirming that the use of volatile anaesthetics was associated with a significant reduction in cardiac troponin I release peak (weighted mean differences –2.35 ng/dl (–3.09, –1.60), $P = 0.00001$) with all 15 studies reporting cardiac biomarker data

Table 2

Intra- and post-operative data of patients who received either volatile anaesthetics (50 patients) or total intravenous anaesthesia (TIVA) (50 patients) to prevent myocardial damage for mitral valve surgery with concomitant coronary artery disease.

Variables	Volatile anaesthetics (n = 50) (%)	TIVA (n = 50) (%)	*P* value
Surgery			
Mitral surgery	48 (96)	50 (100)	0.2
Replacement	18 (36)	16 (32)	0.8
Repair	30 (60)	34 (68)	0.5
Coronary artery bypass graft	37 (74)	40 (80)	0.6
Number of grafts	1 (1–2)	1 (1–2)	0.2
Intra-operative data			
Cardiopulmonary bypass time (in minutes)	104 ± 21	97 ± 27	0.2
Aortic cross-clamp (in minutes)	82 ± 17	77 ± 24	0.3
Fentanyl (in μg)	1347 ± 447	1670 ± 469	0.002
Electrical cardioversion, number of patients	16 (32)	24 (48)	0.2
Intra-operative inotropes	25 (50)	29 (58)	0.5
Left ventricular dysfunction	7 (14)	5 (12)	0.8
Right ventricular dysfunction	4 (8)	4 (8)	0.6
Intra-aortic balloon pump	12 (24)	9 (18)	0.6
Pre-cardiopulmonary bypass	7 (14)	4 (8)	0.3
After cardiopulmonary bypass	2 (4)	1 (2)	0.6
In the intensive care unit (ICU)	3 (6)	4 (8)	0.7
Post-operative data			
Use of inotropic agents	33 (66)	38 (76)	0.3
Dopamine 5 μg/kg/min	10 (20)	18 (36)	0.08
Epinephrine	26 (52)	25 (50)	0.8
Norepinephrine	7 (14)	5 (10)	0.5
Enoximone	18 (36)	11 (22)	0.12
Q wave myocardial infarction	3 (6)	3 (6)	0.7
Haematocrit (ICU arrival)	(37 ± 4.5)	(36 ± 4.0)	0.2
Haematocrit (ICU discharge)	(33 ± 5.2)	(33 ± 4.7)	0.8
Transfusion of blood products, number of patients	12 (24)	13 (26)	0.9
Red blood cell units in patients who received transfusion, median [25th and 75th percentiles]	3 [2–6]	2 [1–4]	0.3
Serum creatinine, mg/dl median [25th and 75th percentiles]			
pre-operative	0.94 [0.79–1.11]	0.96 [0.86–1.07]	0.6
ICU arrival	0.85 [0.70–1.02]	0.91 [0.76–1.03]	0.5
Day I	1.11 [0.87–1.36]	1.10 [0.90–1.45]	0.6
Day II	1.10 [0.90–1.44]	1.13 [0.88–1.37]	0.8
Peak value	1.22 [0.98–1.38]	1.23 [1.00–1.58]	0.8
Renal replacement therapy	2 (4)	2 (4)	0.7
Pneumonia or sepsis	3 (6)	2 (4)	0.5
New onset atrial fibrillation	15 (30)	8 (16)	0.2
Neurological event type I or II	2 (4)	2 (4)	0.7
Mechanical ventilation, hours median [25th and 75th percentiles]	20.5 [12–61.5]	16.5 [12–24]	0.3
ICU stay, days median [25th and 75th percentiles]	3 [1–5]	3 [1–4]	0.3
Length of hospitalisation, days median [25th and 75th percentiles]	8 [6–15]	7 [6–11]	0.5
Tracheostomy	1 (2)	1 (2)	0.7
Death at 30 days	1 (2)	2 (4)	0.5
Death at 1 year	1 (2)	2 (4)	0.5

showing at least a trend toward a reduction in cardiac troponin release in the volatile agents group.

The most recent meta-analysis on this topic (sevoflurane vs. propofol) in cardiac surgery included 13 studies and 696 patients with no difference in post-operative mechanical ventilation time, inotropic support, mortality, myocardial infarction, and atrial fibrillation between the two groups, and benefits were limited to higher post-bypass cardiac index, lower troponin I level, lower incidence of myocardial ischemia, shorter ICU, and hospital length of stay in the sevoflurane group.[27]

No evidence exists on the beneficial effects of high-risk patients, those who are supposed to benefit most from drug pre-conditioning. Interestingly, Jakobsen et al.[22] showed that in high-risk patients undergoing urgent CABG, there is a reduction in mortality with propofol (8.19% in the propofol group vs. 16.23% in the sevoflurane group, $P = 0.031$).

More interestingly, recent guidelines[19] suggested the use of volatile agents in patients undergoing non-cardiac surgery at risk for perioperative myocardial infarction but only in those who are haemodynamically stable.

The beneficial effects of volatile agents in low-risk patients undergoing cardiac surgery has been confirmed by two recent papers.

A meta-regression by Bignami et al.[28] showed that the duration of volatile agents administration bore an inverse correlation with risk-adjusted mortality ratio; the lowest mortality was found in the centres that used them throughout the operation. De Hert et al.[10] showed that sevoflurane administration throughout CABG surgery reduces post-operative troponin release when compared with TIVA or volatile anaesthetics administered only before or after CPB. In the present study, sevoflurane was not administered during CPB, thus losing potential beneficial effects deriving from sevoflurane administration throughout the procedure. Although the standard definition of pharmacologic preconditioning concerns the use of a drug before the onset of ischemic stimulus, it has already been suggested[10] that volatile anaesthetics are effective before ischemia and during reperfusion, with additive effects.

In a recent multi-centre study by De Hert et al.,[11] the authors randomised 414 patients undergoing CABG with CPB to receive a TIVA regimen vs. an inhalational one based on desflurane or sevoflurane. They did not find differences in post-operative troponin release between the two groups but hospital length of stay was reduced in halogenated treated patients. Notably, 1-year mortality was 12.3% in the TIVA group, 3.3% in the sevoflurane group, and 6.7% in the desflurane group. A comparison of mortality curves showed a different pattern between groups ($P = 0.034$). This was the first multi-centre randomised trial to suggest a reduction of mortality in halogenated treated patients. However, this study was underpowered for such an important outcome.

Volatile agents are among the few pharmacological agents that might reduce mortality in cardiac surgery as recently stated by an international consensus conference on this topic.[29,30]

As for other myocardial protection techniques, the difficulty to translate the experimental results into clinical practice needs clarification.[31–33]

Experimental studies were mainly conducted in healthy young male animals, subjected to a similar sustained ischemic time, and anaesthetised with a standardised anaesthetic protocol. Contrary to experimental studies, the clinical setting is characterised by many confounding variables that may interfere:[34] the most important of them being the surgeon skills, length of myocardial ischaemia, anatomy of the coronary arteries, interaction with other medications with a direct or in direct effect on myocardial protection, and type of cardioplegia. Aging also has a negative impact on the efficacy of pre-conditioning, possibly through mitochondrial dysfunction.[35] Female gender confers cardioprotection against ischaemia-reperfusion injury, in part by oestrogen-induced nitric oxide production.[36] Hyperglycemia and diabetes can abrogate the preconditioning phenomenon, while insulin induces both pre- and post-conditioning.[37,38] Concomitant perioperative medication can moreover mix up the message: protection can be enhance by opioids, sildenafil, statins, nitroglycerin, or flumazenil, while some other agents can reverse the cardioprotection such as sulfonylurea drugs, theophylline, or midazolam.[34,39]

Furthermore, there is still no evidence of cardiac protection by volatile agents when administered in the ICU following CABG.[40]

Limitations

Propofol was used as hypnotic in both groups as in other clinical studies. We can not rule out that ROS scavenger properties of propofol may have interfered with our results. Cardiac troponin values could have peaked at different time points, and a more frequent sampling could have showed different results. Furthermore, we acknowledge that the population was heterogeneous, including different surgeries, and that the expected 20% reduction in a marker with a relatively great variation was perhaps too optimistic. It is worth noticing that the propofol group received a higher dose of fentanyl and that opioids have beneficial properties in the field of cardiac surgery: nonetheless, both groups received middle doses of opioids as routinely performed in modern cardiac anaesthesia. It should also be noted that we allowed a wide range of sevoflurane doses while previous studies used fixed doses of volatile agents.

In summary, in this randomised controlled study, it was shown that sevoflurane administered in the pre and post-CPB period does not protect against myocardial damage as documented by cTnI peak release in patients with coronary disease undergoing mitral valve surgery when compared with a propofol-based TIVA.

Acknowledgements

This study was entirely supported by departmental funds. Landoni Giovanni acknowledges receiving modest speaker fees from: Abbott, Baxter, Minrad.

Conflict of interest: None (employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications, and travel grants).

References

1. De Hert SG, Turani F, Mathur S, Stowe DF. Cardioprotection with volatile anesthetics: mechanisms and clinical implications. Anesth Analg 2005; 100: 1584–93.
2. Chiari P, Bouvet F, Piriou V. Anaesthetic-induced myocardial preconditioning: fundamental basis and clinical implications. Ann Fr Anesth Reanim 2005; 24: 383–96.
3. De Hert SG. The concept of anaesthetic-induced cardioprotection: clinical relevance. Best Pract Res Clin Anaesthesiol 2005; 19: 445–59.
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. Yu CH, Beattie WS. The effects of volatile anesthetics on cardiac ischemic complications and mortality in CABG: a meta-analysis. Can J Anaesth 2006; 53: 906–18.
6. Landoni G, Biondi-Zoccai GG, Zangrillo A, Bignami E, D'Avolio S, Marchetti C, Calabrò MG, Fochi O, Guarracino F, Tritapepe L, De Hert S, Torri G. Desflurane and sevoflurane in cardiac surgery: a meta-analysis of randomized clinical trials. J Cardiothorac Vasc Anesth 2007; 21: 502–11.
7. Bignami E, Landoni G, Crescenzi G, Gonfalini M, Bruno G, Pappalardo F, Marino G, Zangrillo A, Alfieri O. Role of cardiac biomarkers (troponin I and CK-MB) as predictors of quality of life and long-term outcome after cardiac surgery. Ann Card Anaesth 2009; 12: 22–6.
8. Landoni G, Bignami E, Oliviero F, Zangrillo A. Halogenated anaesthetics and cardiac protection in cardiac and non-cardiac anaesthesia. Ann Card Anaesth 2009; 12: 4–9.
9. Landoni G, Fochi O, Tritapepe L, Guarracino F, Belloni I, Bignami E, Zangrillo A. Cardiac protection by volatile anesthetics. A review. Minerva Anestesiol 2009; 75: 269–73.
10. De Hert SG, Van der Linden PJ, Cromheecke S, Meeus R, Nelis A, Van Reeth V, ten Broecke PW, De Blier IG, Stockman BA, Rodrigus IE. Cardioprotective properties of sevoflurane in patients undergoing coronary surgery with cardiopulmonary bypass are related to the modalities of its administration. Anesthesiology 2004; 101: 299–310.
11. De Hert S, Vlasselaers D, Barbé R, Ory JP, Dekegel D, Donnadonni R, Demeere JL, Mulier J, Wouters P. A comparison of volatile and non volatile agents for cardioprotection during on-pump coronary surgery. Anaesthesia 2009; 64: 953–60.
12. Story DA, Poustie S, Liu G, McNicol PL. Changes in plasma creatinine concentration after cardiac anesthesia with isoflurane, propofol, or sevoflurane: a randomized clinical trial. Anesthesiology 2001; 95: 842–8.
13. Tritapepe L, Landoni G, Guarracino F, Pompei F, Crivellari M, Maselli D, De Luca M, Fochi O, D'Avolio S, Bignami E, Calabrò MG, Zangrillo A. Cardiac protection by volatile anaesthetics: a multicentre randomized controlled study in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass. Eur J Anaesthesiol 2007; 24: 323–31.
14. Bein B, Renner J, Caliebe D, Scholz J, Paris A, Fraund S, Zaehle W, Tonner PH. Sevoflurane but not propofol preserves myocardial function during minimally invasive direct coronary artery bypass surgery. Anesth Analg 2005; 100: 610–6.
15. Conzen PF, Fischer S, Detter C, Peter K. Sevoflurane provides greater protection of the myocardium than propofol in patients undergoing off-pump coronary artery bypass surgery. Anesthesiology 2003; 99: 826–33.
16. Guarracino F, Landoni G, Tritapepe L, Pompei F, Leoni A, Aletti G, Scandroglio AM, Maselli D, De Luca M, Marchetti C, Crescenzi G, Zangrillo A. Myocardial damage prevented by volatile anesthetics: a multicenter randomized controlled study. J Cardiothorac Vasc Anesth 2006; 20: 477–83.
17. Landoni G, Calabrò MG, Marchetti C, Bignami E, Scandroglio AM, Dedola E, De Luca M, Tritapepe L, Crescenzi G, Zangrillo A. Desflurane versus propofol in patients undergoing mitral valve surgery. J Cardiothorac Vasc Anesth 2007; 21: 672–7.
18. Cromheecke S, Pepermans V, Hendrickx E, Lorsomradee S, Ten Broecke PW, Stockman BA, Rodrigus IE, De Hert SG. Cardioprotective properties of sevoflurane in patients undergoing aortic valve replacement with cardiopulmonary bypass. Anesth Analg 2006; 103: 289–96.
19. 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, Buller CE, Creager MA, Ettinger SM, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Nishimura R, Ornato 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. J Am Coll Cardiol 2007; 50: 1707–32.
20. Landoni G, Fochi O, Bignami E, Calabrò MG, D'Arpa MC, Moizo E, Mizzi A, Pappalardo F, Morelli A, Zangrillo A. Cardiac protection by volatile anesthetics in non-cardiac surgery? A meta-analysis of randomized controlled studies on clinically relevant endpoints. HSR Proc Intensive Care Cardiovasc Anesth 2009; 4: 34–43.
21. Landoni G, Zangrillo A, Fochi O, Maj G, Scandroglio AM, Morelli A, Tritapepe L, Montorfano M, Colombo A. Cardiac protection with volatile anesthetics in stenting procedures. J Cardiothorac Vasc Anesth 2008; 22: 543–7.
22. Jakobsen CJ, Berg H, Hindsholm KB, Faddy N, Sloth E. The influence of propofol versus sevoflurane anesthesia on outcome in 10,535 cardiac surgical procedures. J Cardiothorac Vasc Anesth 2007; 21: 664–71.
23. Lamberts RR, Onderwater G, Hamdani N, Vreden MJ, Steenhuisen J, Eringa EC, Loer SA, Stienen GJ, Bouwman RA. Reactive oxygen species-induced stimulation of 5'AMP-activated protein kinase mediates sevoflurane-induced cardioprotection. Circulation 2009; 120: S10–5.
24. Landoni G, Fochi O, Bignami E, De Simone F, Zangrillo A. Volatile anesthetics for periprocedural cardiac protection. A review. Minerva Cardioangiol 2008; 56: 429–34.
25. Thygesen K, Alpert JS, White HD. Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction: consensus conference for the universal definition of myocardial infarction. Circulation 2007; 116: 2634–53.
26. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. Circulation 1986; 74: 1124–36.
27. Yao Y-T, Li L-H. Sevoflurane versus propofol for myocardial protection in patients undergoing coronary artery bypass grafting surgery: a meta-analysis of randomized controlled trials. Chin Med Sci J 2009; 24: 133–41.

28. Bignami E, Biondi-Zoccai G, Landoni G, Fochi O, Testa V, Sheiban I, Giunta F, Zangrillo A. Volatile anesthetics reduce mortality in cardiac surgery. J Cardiothorac Vasc Anesth 2009; 23: 594–9.
29. Landoni G, Augoustides JG, Guarracino F, Santini F, Ponschab M, Pasero D, Rodseth RN, Biondi-Zoccai G, Silvay G, Salvi L, Camporesi E, Comis M, Conte M, Bevilacqua S, Cabrini L, Cariello C, Caramelli F, De Santis V, Del Sarto P, Dini D, Forti A, Galdieri N, Giordano G, Gottin L, Greco M, Maglioni E, Mantovani L, Manzato A, Meli M, Paternoster G, Pittarello D, Rana KN, Ruggeri L, Salandin V, Sangalli F, Zambon M, Zucchetti M, Bignami E, Alfieri O, Zangrillo A. Mortality reduction in cardiac anesthesia and intensive care: results of the first International Consensus Conference. Acta Anaesthesiol Scand 2011; 55: 259–66.
30. Landoni G, Augoustides JG, Guarracino F, Santini F, Ponschab M, Pasero D, Rodseth RN, Biondi-Zoccai G, Silvay G, Salvi L, Camporesi E, Comis M, Conte M, Bevilacqua S, Cabrini L, Cariello C, Caramelli F, De Santis V, Del Sarto P, Dini D, Forti A, Galdieri N, Giordano G, Gottin L, Greco M, Maglioni E, Mantovani L, Manzato A, Meli M, Paternoster G, Pittarello D, Rana KN, Ruggeri L, Salandin V, Sangalli F, Zambon M, Zucchetti M, Bignami E, Alfieri O, Zangrillo A. Mortality reduction in cardiac anesthesia and intensive care: results of the first International Consensus Conference. HSR proceedings in intensive care and cardiovascular anesthesia. 2011; 3: 9–19.
31. Bolli R, Becker L, Gross G, Mentzer R Jr, Balshaw D, Lathrop DA. Myocardial protection at a crossroads: the need for translation into clinical therapy. Circ Res 2004; 95: 125–34.
32. Larsen JR, Smerup M, Hasenkam JM, Christensen SD, Sivesgaard K, Torp P, Sloth E. Hypertrophied hearts: what of sevoflurane cardioprotection? Acta Anaesthesiol Scand 2009; 53: 496–504.
33. Pesonen E. Editorial: cardiac pre- and post-conditioning: implications in anesthesia? Acta Anaesthesiol Scand 2010; 54: 793–4.
34. Zaugg M. Is protection by inhalation agents volatile? Controversies in cardioprotection. Br J Anaesth 2007; 99: 603–6.
35. Mio Y, Bienengraeber MW, Marinovic J, Gutterman DD, Rakic M, Bosnjak ZJ, Stadnicka A. Age-related attenuation of isoflurane preconditioning in human atrial cardiomyocytes: roles for mitochondrial respiration and sarcolemmal adenosine triphosphate-sensitive potassium channel activity. Anesthesiology 2008; 108: 612–20.
36. Wang C, Chiari PC, Weihrauch D, Krolikowski JG, Warltier DC, Kersten JR, Pratt PF Jr. Pagel PS: gender-specificity of delayed preconditioning by isoflurane in rabbits: potential role of endothelial nitric oxide synthase. Anesth Analg 2006; 103: 274–80.
37. Tanaka K, Kehl F, Gu W, Krolikowski JG, Pagel PS, Warltier DC, Kersten JR. Isoflurane-induced preconditioning is attenuated by diabetes. Am J Physiol Heart Circ Physiol 2002; 282: H2018–23.
38. Jonassen AK, Sack MN, Mjos OD, Yellon DM. Myocardial protection by insulin at reperfusion requires early administration and is mediated via Akt and p70s6 kinase cell-survival signaling. Circ Res 2001; 89: 1191–8.
39. Rivo J, Raphael J, Drenger B, Berenshtein E, Chevion M, Gozal Y. Flumazenil mimics whereas midazolam abolishes ischemic preconditioning in a rabbit heart model of ischemia-reperfusion. Anesthesiology 2006; 105: 65–71.
40. Hellström J, Öwall A, Bergström J, Sackey PV. Cardiac outcome after sevoflurane versus propofol sedation following coronary bypass surgery: a pilot study. Acta Anaesthesiol Scand 2011; 55: 460–7.

Address:
Landoni Giovanni
Department of Cardiothoracic Anesthesia and Intensive Care
Istituto Scientifico San Raffaele
Via Olgettina 60
20132 Milano
Italy
e-mail: landoni.giovanni@hsr.it