

# Sevoflurane Versus Total Intravenous Anesthesia for Isolated Coronary Artery Bypass Surgery With Cardiopulmonary Bypass: A Randomized Trial



Valery V. Likhvantsev, MD,\* Giovanni Landoni, MD,† Dmitry I. Levikov, PhD,‡ Oleg A. Grebenchikov, PhD,\* Yuri V. Skripkin, MD,\* and Rostislav A. Cherpakov, MD§

**Objective:** Several studies have suggested that the cardioprotective effects of halogenated anesthetics in cardiac surgery result in reduced cardiac biomarker release compared with total intravenous anesthesia (TIVA). These findings came from relatively small randomized clinical trials and meta-analyses. The authors of this study hypothesized that the beneficial effects of volatile anesthetics translate into a reduced length of hospital stay after coronary artery bypass grafting surgery (CABG) with cardiopulmonary bypass.

**Design:** A randomized controlled trial.

**Setting:** Two university hospitals.

**Participants:** Adult patients undergoing elective CABG surgery with cardiopulmonary bypass.

**Interventions:** Patients were assigned randomly to 2 following groups: propofol-based TIVA group (n = 431) and sevoflurane group (n = 437).

**Measurements and Main Results:** The primary endpoint was hospital length of stay, and the secondary endpoint included postoperative troponin T and N-terminal pro-brain

natriuretic peptide release and mortality. In the sevoflurane group, a reduced length of hospital stay was observed compared with the propofol-based TIVA group (10 [9–11] days v 14 [10–16],  $p < 0.001$ ) as were reductions in cardiac troponin T release (0.18 ng/mL v 0.57 ng/mL at 24 hours,  $p < 0.001$ ), in N-terminal pro-brain natriuretic peptide release (633 pg/mL v 878 pg/mL at 24 hours,  $p < 0.001$ ; 482 pg/mL v 1,036 pg/mL at 48 hours,  $p < 0.001$ ), and in mortality at 1-year follow up (17.8% v 24.8%,  $p = 0.03$ ).

**Conclusions:** Anesthesia with sevoflurane reduced cardiac biomarker release and length of hospital stay after CABG with cardiopulmonary bypass surgery compared with propofol-based TIVA with a possible reduction in 1-year mortality.

© 2016 Elsevier Inc. All rights reserved.

**KEY WORDS:** anesthesia, inhalation anesthesia, sevoflurane, intravenous anesthesia, cardiac surgery, survival analysis, mortality

APPROXIMATELY 1 MILLION cardiac surgery procedures are performed every year worldwide.<sup>1</sup> In the United States alone about 200,000 coronary artery bypass procedures are performed annually.<sup>2</sup> Morbidity and mortality<sup>3</sup> frequently are caused by insufficient cardioprotection from ischemia/reperfusion injury. Cardioplegia and optimization of hemodynamics traditionally are used to minimize complications.<sup>4,5</sup> Recent findings suggest that volatile anesthetics provide a cardioprotective effect with pharmacologic mechanisms of action that are only partially related to the anesthetic effects on the myocardial oxygen balance.<sup>6</sup> The molecular mechanisms for the implementation of the cardioprotective effect of halogenated anesthetics are similar to those that contribute to ischemic preconditioning. By analogy, this effect has been named as “pharmacologic preconditioning by volatile anesthetics” or “anesthetic preconditioning”.<sup>7</sup>

Numerous studies have attempted to clarify the clinical efficacy of anesthetic preconditioning,<sup>8–10</sup> and this approach has been associated with a decreased level of myocardial damage markers<sup>11,12</sup> and improvement of the hemodynamic parameters<sup>11,13,14</sup> in different types of cardiac surgery, especially in coronary artery bypass grafting (CABG) surgery, compared with total intravenous techniques (TIVA).<sup>13,15,16</sup> Nonetheless, a number of studies failed to confirm these findings, and this subject remains highly controversial.<sup>17,18</sup>

Few studies on the effect of anesthetic preconditioning have collected data on long-term survival,<sup>19–21</sup> and meta-analyses have had contrasting findings.<sup>22–24</sup>

Part of the reason for the conflicting data published so far probably was due to the concomitant use of propofol in most trials. There are experimental data about a possible inhibitory action of propofol on the cardioprotective effect of volatile anesthetics.<sup>25,26</sup> Furthermore, all the findings published

to date came from small or middle-sized trials and meta-analyses.

Volatile agents contribute to perioperative organ protection (mostly cardiac protection), reduce the need for inotropic agents, and preserve cardiac function after cardiac surgery.<sup>9,27</sup> This could improve not only cardiac function but also other organ perfusion, and it could improve recovery from postoperative myocardial stunning in cardiac surgery, resulting in a reduced length of hospital stay (LOS). This has been suggested in previous studies<sup>23</sup> but never confirmed in a large randomized controlled trial (RCT). LOS itself could be considered a composite endpoint of all relevant complications that occur postoperatively. The aim of this study, therefore, was to determine whether the beneficial effects of volatile anesthetics translate into a reduced LOS stay after CABG surgery with cardiopulmonary bypass (CPB).

---

From the \*Anesthesiology and Intensive Care Department, Moscow Regional Research and Clinical Institute, Moscow, Russia; †Anesthesiology and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy, and Vita-Salute San Raffaele University, Milan, Italy; ‡Cardiology Intensive Care Unit, V.A. Negovsky Research Institute of Reanimatology, Moscow, Russia; and §Anesthesiology and Intensive Care Department, V.A. Negovsky Research Institute of Reanimatology, Moscow, Russia.

G. L. acknowledges receiving modest speaker fees from AbbVie, Chicago, IL.

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

© 2016 Elsevier Inc. All rights reserved.

1053-0770/2601-0001\$36.00/0

<http://dx.doi.org/10.1053/j.jvca.2016.02.030>

## METHODS

The study was approved by the local ethical committees of the 2 participating hospitals (No. 0512 Ethics Committee of The Negovsky Reanimatology Research Institute, Moscow, Russia and No. 10 Independent Ethics Committee of the Moscow Regional Research and Clinical Institute, Moscow, Russia), and written, informed consent was obtained from all patients. Patients scheduled to undergo elective, isolated, multiple ( $\geq 2$  grafts) CABG surgery with CPB were included unless there was documented evidence of a recent ( $< 6$  months) or ongoing myocardial infarction or if combined surgical procedures (including valve or ascending aorta procedures) or redo-operations were scheduled. Patients with planned off-pump CABG surgery were excluded. A randomization with numbered, sealed, opaque envelope in each center was used to assign patients to 1 of the following 2 groups: propofol-based TIVA group ( $n = 431$ ) and sevoflurane group ( $n = 437$ ).

The control group received TIVA throughout the surgery. Propofol, fentanyl, and cisatracurium were used for induction and maintenance of general anesthesia with dosages at the discretion of the attending clinician. The only absolute criterion for this group was that no volatile anesthetic was used at any time during the procedure. Propofol was administered to maintain bispectral index (BIS) values in the range of 40 to 60, and fentanyl was administered to avoid changes of mean arterial pressure (MAP) within 20% from baseline but not less than 65 mmHg.

The induction of general anesthesia in the treatment group was left to the discretion of the attending anesthesiologist and consisted of fentanyl and cisatracurium plus either propofol or sevoflurane. The volatile anesthesia induction was performed with sevoflurane, 5% in 100% oxygen, administered through a facial mask with fresh gas flow of 5 L/min until loss of consciousness (guided by BIS values  $< 65$ ) and then reduced to 2% approximately after 4-to-5 minutes. The anesthesia maintenance in the treatment group consisted of sevoflurane at a minimum end-tidal concentration of at least 1 minimal alveolar concentration throughout the entire procedure, including CPB, and was guided using BIS values between 40 and 60. During CPB, sevoflurane was administered in the oxygenator circuit through a calibrated vaporizer and the minimal alveolar concentration was measured at the outlet of the oxygenator of the extracorporeal circulation. Fentanyl was administered to avoid changes of MAP within 20% from baseline but not less than 65 mmHg.

Beta-blockers and aspirin were continued until the morning of surgery in all patients, and sulfonyleurea was stopped and replaced with insulin at the time of hospital admission.

All patients were mechanically ventilated in continuous mandatory volume ventilation mode. Intraoperative continuous monitoring included 5-lead electrocardiography with ST analysis, heart rate, invasive blood pressure, pulse oximetry, body temperature, tidal/minute volume, fraction of inspired oxygen ( $F_{iO_2}$ ), fraction of end-tidal carbon dioxide, inspired/end-tidal sevoflurane concentration, central venous pressure, and BIS in all patients of both groups. Pulmonary artery pressure, wedge

pressure and cardiac output were measured in patients with an ejection fraction  $< 50\%$ .

All patients underwent CABG with CPB using Jostra HL20 (Maquet, Rastatt, Germany) and Stroker HLM Cobe (Sorin Group, Milan, Italy) heart-lung machines with a roller pump for nonpulsatile perfusion and membrane oxygenators with a flow rate of 2.4 L/min/m<sup>2</sup> at 32°C of central body temperature. Cardioplegia was achieved using Consol (Samson-Med Ltd, St. Petersburg, Russia) or Custodiol (Dr. Franz Köhler Chemie, GmbH, Bensheim, Germany) solutions. Four surgeons were involved in the study period as first operators.

At CPB weaning, dobutamine (starting dose 5  $\mu\text{g}/\text{kg}/\text{min}$  with increments of 1  $\mu\text{g}/\text{kg}/\text{min}$  until the desired MAP level was reached) was administered when anesthetic agents were at minimum valid levels as guided by BIS, filling pressures were high, and cardiac index (CI) was  $< 2.0$  L/min/m<sup>2</sup>. If the CI remained  $< 2.0$  L/m<sup>2</sup>/min with dobutamine (initial doses of 5  $\mu\text{g}/\text{kg}/\text{min}$ ), norepinephrine was added (starting dose of 0.02  $\mu\text{g}/\text{kg}/\text{min}$ , with increments of 0.02  $\mu\text{g}/\text{kg}/\text{min}$  until the desired MAP level was reached).

Postoperative low-cardiac-output syndrome (LCOS) was defined as CI  $< 2.2$  L/min/m<sup>2</sup>, pulmonary capillary pressure  $\geq 16$  mmHg, and mixed venous saturation  $< 60\%$ . Diagnosis of LCOS was performed after excluding or correcting temperature anomalies (hypothermia), hypovolemia, cardiac rhythm abnormalities (eg, bradycardia), cardiac tamponade, or myocardial ischemia. In patients experiencing LCOS, dobutamine was started at a dose of 5  $\mu\text{g}/\text{kg}/\text{min}$ , and if a hemodynamic response was not observed, the dose was increased to 7.5, 10, and finally to 12.5  $\mu\text{g}/\text{kg}/\text{min}$  at 15-minute intervals. In patients in whom low cardiac output persisted, epinephrine was added as a second inotropic drug at a dose of 0.02 to 0.1  $\mu\text{g}/\text{kg}/\text{min}$ .

Criteria for extubation were partial pressure of oxygen/ $F_{iO_2} > 250$ , respiratory rate  $\leq 25$ , arterial oxygen saturation = 98% to 100% at  $F_{iO_2} = 0.4$  for 1 hour. Criteria for intensive care unit discharge were spontaneous breathing, hemodynamic stability without inotropic treatment, clear consciousness, and normal renal function. The discharge was decided by doctors not involved in the study.

Hospital discharge criteria were hemodynamic and cardiac rhythm stability, the absence of incision site infection, an afebrile condition, normal bowel movements, and independent ambulation and feeding. Standard discharge medications after CABG were beta-blockers, statins, and low-dose aspirin. The discharge time was managed by surgeons not involved in the trial.

The primary endpoint of the study was LOS. Secondary endpoints included myocardial cell damage quantified by troponin T release 24 hours after surgery; N-terminal pro-brain natriuretic peptide (NT-proBNP) release 24 and 48 hours after surgery; and 7-day, 30-day, and 1-year mortality. Samples were centrifuged and plasma was frozen at 40°C before they were centrally analyzed.

Sample-size calculation was based on a 2-sided alpha error of 0.05 and 0.9 power. On the basis of data from their centers, the authors predicted a mean LOS of  $15 \pm 9$  days in the TIVA group and considered a reduction of 2 days in the sevoflurane group as clinically relevant. The authors calculated that

427 patients per group would be needed and planned to randomly select 900 patients to take into account possible protocol deviations. Data between groups were compared using the chi-square, analysis of variance, or Mann-Whitney tests as appropriate; for variables with more than 1 measurement, analysis of variance for repeated measurement was performed. The normality of variables distribution was estimated using the Shapiro-Wilk *W* test and the Lilliefors test. The distribution was considered as normal at  $p > 0.05$ . When results of tests were different, the Shapiro-Wilks *W* test was preferred. No adjustment was made for data or significance level (accepted  $p < 0.05$ ) for multiplicity of measurement. Differences between the sevoflurane and TIVA groups were assessed using univariate and multivariate regression analysis. For the univariate analysis the cut-off level for significance was set at  $p < 0.05$ . Multivariate regression analyses were performed for LOS (with a classic linear regression) and for mortality at different follow-up periods (with logistic regression). All regression models were performed using stepwise selection. The preoperative and intraoperative clinical data were entered into the model if they had a univariate  $p$  value of  $< 0.2$ . Treatment group (sevoflurane *v* TIVA) always was forced into the multivariate model. In the multivariate analyses, clinical factors or potential confounding variables were expressed as odds ratio with a 95% confidence interval for the mortality analyses and as point estimation with a 95% confidence interval for LOS. Data were analyzed using the Stata Statistical Software: Release 13 (StataCorp, College Station, TX).

Data are expressed as means and standard deviation or median and interquartile ranges as appropriate. Statistical significance was set at  $p < 0.05$ . Data were analyzed according to a modified intention-to-treat analysis (for logistical reasons the redo surgeries were excluded after randomization).

## RESULTS

A total of 900 patients were recruited between September 2012 and April 2014 (450 patients were randomly assigned to receive TIVA and 450 to receive sevoflurane). Patients who were discovered after randomization to be redo surgeries (19 TIVA and 13 sevoflurane patients) did not receive the allocated treatment and were excluded from analyses (Fig 1).

No differences were observed between groups at baseline (before randomization) (Table 1). No protocol deviation was reported.

In the TIVA group patients received propofol,  $2.2 \pm 0.5$  mg/kg, and fentanyl, 4  $\mu$ g/kg, in boluses at induction of anesthesia; a continuous infusion of propofol,  $3.7 \pm 1.1$  mg/kg/h, and fentanyl, 3 to 4  $\mu$ g/kg, in boluses before and after CPB; and propofol,  $4.5 \pm 0.5$  mg/kg/h, and fentanyl,  $5.7 \pm 1.0$   $\mu$ g/kg/h, in boluses during CPB.

In the sevoflurane group, induction of general anesthesia was performed with fentanyl, 1  $\mu$ g/kg, in boluses with either sevoflurane mask induction in 168 patients or with fentanyl, 4  $\mu$ g/kg, and propofol, ( $2.3 \pm 0.3$  mg/kg), in 269 patients. Anesthesia maintenance was performed in all patients of this group with sevoflurane plus fentanyl,  $1.9 \pm 1.0$  mg/kg/h, in boluses before and after CPB and with fentanyl,  $3.5 \pm 0.5$   $\mu$ g/kg/h, in boluses during CPB.

A reduction in LOS in the sevoflurane group compared with the propofol group was found in the overall enrolled population and when analyzing only the patients who survived throughout their hospital stay (Table 2). A multivariate analysis confirmed that TIVA was the strongest independent predictor of prolonged LOS followed by high NT-proBNP, low ejection fraction, previous myocardial infarction, and high EuroSCORE II (Supplemental Table 1). No difference in LOS between the 2 centers was noted ( $p = 0.15$ ).

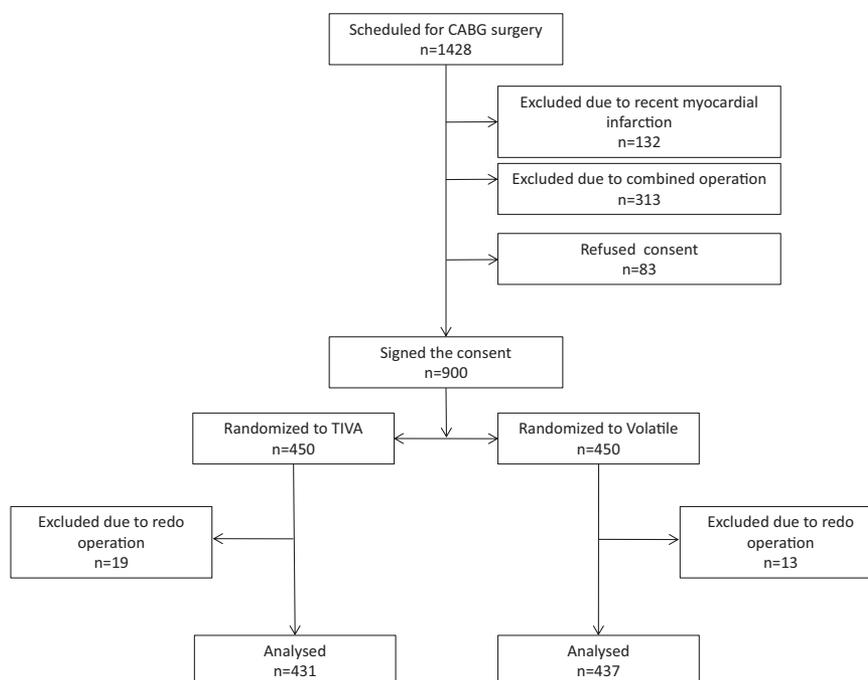


Fig 1. Flowchart for treatment groups. CABG, coronary artery bypass grafting; TIVA, total intravenous anesthesia.

**Table 1. Baseline and Intraoperative Data in Patients Randomly Assigned to Receive Propofol-Based Total Intravenous Anesthesia or Sevoflurane**

	TIVA Group (n = 431)	Sevoflurane Group (n = 437)	p Value
<b>Preoperative data</b>			
Sex, male, n (%)	384 (89%)	380 (87%)	0.33
Age, years, mean (SD)	61 (8)	62 (8)	0.50
Weight, kg, mean (SD)	86 (8)	87 (8)	0.068
Ejection fraction, mean (SD)	55 (7)	54 (6)	0.11
Previous myocardial infarction, n (%)	340 (79%)	328 (75%)	0.18
Arrhythmia (other than sinus or premature atrial contractions), n (%)	32 (7.4%)	35 (8.0%)	0.75
Diabetes mellitus, n (%)	82 (19%)	66 (15%)	0.12
EuroSCORE II, median (IQR)	0.75 (0.63-0.90)	0.77 (0.65-0.91)	0.29
NT-proBNP, pg/mL, median (IQR)	270 (138-473)	250 (138-426)	0.12
<b>Intraoperative data</b>			
Surgery duration, min	299 (61)	292 (53)	0.099
Cardiopulmonary bypass time, min	71 (17)	72 (16)	0.55
Aortic clamp time, min	43 (11)	44 (12)	0.19
Distal grafts, median (interquartile range)	3 (2-3)	3 (2-3)	0.93

NOTE. Data are presented as mean (SD) unless noted otherwise.

Abbreviations: IQR, interquartile range; NT-proBNP, N-terminal pro-brain natriuretic peptide; SD, standard deviation; TIVA, total intravenous anesthesia.

Troponin T at 24 hours was reduced significantly (by approximately 50%) in the sevoflurane group compared with the TIVA group (see Table 2). NT-proBNP at 24 and 48 hours was reduced significantly (again by approximately 50%) in the sevoflurane group compared with the TIVA group (see Table 2).

Seven-day mortality was 6/437 (1.4%) in the sevoflurane group versus 8/431 (1.9%) in the TIVA group ( $p = 0.57$ ). One-month mortality was 17/437 (3.9%) in the sevoflurane group versus 20/431 (4.6%) in the TIVA group ( $p = 0.58$ ). One-year mortality was 52/292 (17.8%) in the sevoflurane group versus 81/326 (24.8%) in the TIVA group ( $p = 0.03$ ). A multivariate analysis confirmed that TIVA was an independent predictor of mortality at 1 year and at 30 days but not at 7 days (Supplemental Tables 2–4). No difference in mortality between the 2 centers was noted ( $p = 0.7$  at 7 days;  $p = 0.5$  at 30 days;  $p = 0.12$  at 1 year).

The avoidance of propofol (performing the analyses in patients who never received propofol v patients who received propofol at anesthesia induction only or throughout all the anesthesia) was associated with a reduction in cardiac biomarkers and in LOS, with a trend toward reduced mortality (Table 3).

Addition of propofol for anesthesia induction in patients randomly assigned to sevoflurane anesthesia was associated

with higher postoperative troponin T and NT-proBNP release after 24 hours, with a reduction in LOS, and with a trend toward increased mortality (Table 4).

## DISCUSSION

This study confirmed that sevoflurane-based anesthesia for CABG surgery with CPB was, associated with cardiac protection and a reduced LOS. This has been the largest RCT performed so far on this topic (TIVA v halogenated anesthetics in the perioperative period of any surgery), and these findings were in agreement with previously published trials.<sup>12,16,28</sup>

Interestingly, an important point of this study was the confirmation that the cardioprotective properties of volatile agents might extend outside the perioperative period, with a trend toward a reduction in mortality in patients receiving sevoflurane. Because this was an RCT, the differences in outcomes had to be attributed to the different anesthesia plan. Few other published manuscripts have suggested that volatile agents could have long-term effects. In a way similar to ischemic preconditioning, volatile anesthetics can trigger an acute cardioprotective memory effect that lasts beyond their elimination. This effect lasts not only for the “first” and “second” classical preconditioning windows, but it may affect late cardiac events and outcome. Garcia et al,<sup>29</sup> for example,

**Table 2. Cardiac Biomarkers and Length of Hospital Stay in Patients Randomly Assigned to Receive Propofol-Based Total Intravenous Anesthesia or Sevoflurane**

	TIVA Group (n = 431)	Sevoflurane Group (n = 437)	p Value
Troponin T after 24 h, ng/mL	0.57 (0.12-0.91)	0.18 (0.12-0.35)	<0.001
NT-proBNP after 24 h, pg/mL	878 (561-1,825)	633 (452-1,105)	<0.001
NT-proBNP after 48 h, pg/mL	1,036 (692-2,496)	482 (240-684)	<0.001
Hospital stay, days	14 (10-16)	10 (9-11)	<0.001
Hospital stay in survivors, days	14 (11-16)	10 (9-11)	<0.001

NOTE. Data are presented as median (interquartile range).

Abbreviations: NT-proBNP, N-terminal pro-brain natriuretic peptide; TIVA, total intravenous anesthesia.

**Table 3. Cardiac Biomarkers, Length of Hospital Stay, and Mortality in Patients Who Received Propofol and in Patients Who Received No Propofol\***

Subgroup	7-day Mortality	1-month Mortality	1-year Mortality	Hospital Stay	Troponin T After 24 h, ng/mL	NT-proBNP After 24 h, pg/mL	NT-proBNP After 48 h, pg/mL
With propofol, n = 700	2.0%	4.7%	22.7%	11 (10-14)	0.36 (0.13-0.78)	807 (535-1,574)	711 (514-1,542)
Without propofol, n = 168	0%	2.4%	16.5%	10 (9-10)	0.18 (0.11-0.30)	547 (393-880)	432 (228-668)
p value	0.085	0.21	0.15	<0.01	<0.01	<0.01	<0.01

NOTE. Data are presented as percentages or as median (interquartile range).

Abbreviation: NT-proBNP, N-terminal pro-brain natriuretic peptide.

\* Patients who received propofol were assigned randomly to receive propofol or were assigned randomly to receive sevoflurane but received propofol at anesthesia induction (as allowed by the protocol); patients who received no propofol were assigned randomly to receive sevoflurane and did not receive propofol at anesthesia induction (mask induction with sevoflurane in addition to fentanyl and cisatracurium followed by sevoflurane anesthesia was used).

suggested that late (1 year) cardiac events were higher in patients receiving TIVA compared with those receiving sevoflurane. De Hert et al<sup>20</sup> found no difference in short-term mortality between groups randomly assigned to receive TIVA or sevoflurane, but the 1-year mortality was 12.3% in the TIVA group and 3.3% in the sevoflurane group. Another possibility is that the effect on long-term survival simply is associated with the fact that perioperative cardiac damage (documented by cardiac troponin and NT-proBNP release) consequently affects late cardiac outcomes and mortality.

Other data on survival can be compared only with meta-analyses and, in particular, from a recently published Bayesian network meta-analysis.<sup>23</sup> This analysis found that the use of halogenated agents was associated with a 50% reduction in mortality compared with TIVA at the longest follow-up available.

The data regarding the reduction in postoperative cardiac troponin and NT-proBNP release also are extremely important because these are objective measurements strongly associated with adverse postoperative outcomes.<sup>30</sup>

An intriguing finding of the study presented here was that it also confirmed the hypothesis that propofol inhibits the cardioprotective properties of volatile agents and therefore is associated with an increased release of cardiac biomarkers and a trend toward increased postoperative mortality. In fact, the authors noted differences in cardiac biomarker release and trends in clinically relevant outcomes in patients who did or did not receive propofol at anesthesia induction. This was suggested recently in animal studies<sup>25,26</sup> and could be the reason for conflicting evidence in the field of perioperative cardiac protection in previous trials. A large meta-analysis of RCTs

recently showed nonsignificant trends toward an increased mortality in most of the identified subgroups that received propofol.<sup>27</sup>

As a consequence, the best anesthesia technique in the authors' setting was a sevoflurane-based anesthesia with sevoflurane mask induction, which allowed for the avoidance of propofol administration. This technique is widely used in children and has been described in adult patients undergoing CABG surgery.<sup>31</sup>

Notably, this study was limited to patients undergoing CABG with standard CPB, and patients who had a recent or ongoing myocardial infarction were excluded. In fact, patients undergoing off-pump CABG and those with recent or ongoing myocardial infarction receive fewer or no cardiac protective benefits from volatile agents. This increased the chances of obtaining positive results and, at the same time, reduced the generalizability of these findings.

It should be acknowledged that sevoflurane anesthesia was compared with propofol-based TIVA without strict preconditioning or postconditioning protocols (sevoflurane was administered continuously in the study presented here without regard to the timing of the ischemic insult), and patients who underwent cardiac surgery were elderly and experienced several coexisting diseases that are known to abolish preconditioning and postconditioning phenomena. Nonetheless, volatile agents have organ protective properties that go beyond preconditioning and postconditioning, and even if their effect is not always reproducible in clinical studies as described by recent reviews,<sup>17,18</sup> their effect is promising and, in the opinion of the authors, they either should be used or studied.

**Table 4. Cardiac Biomarkers, Length of Hospital Stay, and Mortality in Patients Randomly Assigned to Receive Sevoflurane Divided into 2 Groups According to Administration of Anesthesia**

Anesthesia	7-day Mortality	1-month Mortality	1-year Mortality	Hospital Stay	Troponin T After 24 h, ng/mL	NT-proBNP After 24 h, pg/mL	NT-proBNP After 48 h, pg/mL
Propofol at anesthesia induction, then sevoflurane, n = 269	2.2%	4.8%	18.6%	10 (10-11)	0.19 (0.13-0.36)	721 (517-1,192)	514 (257-686)
Only sevoflurane throughout the entire surgery, n = 168*	0%	2.4%	16.5%	10 (9-10)	0.18 (0.11-0.30)	547 (393-880)	432 (228-668)
p value	0.087	0.31	0.64	<0.01	0.03	<0.01	0.15

NOTE. Data are presented as percentages or median (interquartile range).

Abbreviation: NT-proBNP, N-terminal pro-brain natriuretic peptide.

\* Administration of anesthesia was via mask induction with sevoflurane in addition to fentanyl and cisatracurium followed by sevoflurane anesthesia or via sevoflurane anesthesia only.

In the field of perioperative cardiac protection, volatile anesthetics share some of the mechanisms of action of the remote ischemic preconditioning technique. This is a promising strategy that had initial positive findings on cardiac<sup>32</sup> and renal biomarker reduction,<sup>33</sup> with a network meta-analysis of RCTs suggesting that the effects on survival are additive between volatile agents and the remote ischemic preconditioning technique.<sup>34</sup> Two large, recent, pragmatic multicenter RCT<sup>35,36</sup> found no cardiac or renal protective effects and no differences in mortality when the remote ischemic preconditioning technique was used in propofol-based cardiac anesthesia. Because the two promising trials<sup>32,33</sup> did not use propofol in their anesthetic plan, it is reasonable to consider that the differences in these findings were due to the use of propofol.<sup>37</sup> This was in accordance with the findings of the study presented here, in which the use of propofol at anesthesia induction only was sufficient to reduce (but not avoid) the beneficial effects of the volatile anesthetics.

### Study Limitations

The study included patients undergoing only CPB and CABG, and the results cannot be extended to other cardiac surgery procedures. Loss to follow-up at 1 year did not allow for definitive conclusions on long-term survival, and unfortunately the study did not include the collection of the following data: the causes of death, date of death (this would have allowed for a Kaplan Meier survival plot), and the need for new hospitalizations or surgeries. The authors also acknowledge that 1-year mortality was extremely high in this cohort of patients. Because the surgical mortality was within international standards, the authors' hypotheses to explain these findings was that patients' adherence to cardiologic medication was extremely poor after hospital discharge and that smoking and alcohol habits likely were resumed very early after cardiac surgery. Nonetheless, this study was the largest one examining this issue to date. The authors also collected few demographic, baseline variables (eg, the numbers of diseased vessels and the

magnitude of stenosis severity in each group and baseline and discharge medications), and intraoperative variables (eg, the propofol and fentanyl concentrations, systemic and pulmonary hemodynamics, doses of inotropic drugs) were not measured and recorded.

This was a randomized pragmatic study that compared 2 anesthesia techniques that are performed daily worldwide in real-life practice. The large number of patients randomly assigned to the 2 groups nonetheless was effective in creating 2 balanced groups, as documented by the data presented in [Table 1](#). Furthermore, the LOS after CABG surgery might appear excessive in both groups of this study, but LOS > 10 days was not unusual in published trials<sup>38,39,40</sup> and could depend, at least in part, on insurance policies, destination of the patients (rehabilitations *v* home), local protocols, guidelines, medical skills, and patient comorbidities and behaviors. The authors also acknowledge that standard doses of drugs at anesthesia induction were not used and that the possibility of administering propofol at induction of anesthesia in the volatile anesthetics group was allowed.

### CONCLUSION

In conclusion, in the largest RCT performed so far, the cardioprotective properties of sevoflurane in cardiac surgery in terms of cardiac biomarker release and reduced LOS was confirmed. The authors also hypothesized that propofol inhibited these cardioprotective properties in the perioperative period of CABG surgery. A large, multicenter, multinational trial is warranted to confirm that long-term survival is affected significantly by the choice of anesthetic.

### APPENDIX A. SUPPLEMENTARY MATERIAL

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1053/j.jvca.2016.02.030>.

### REFERENCES

- Herbertson M: Recombinant activated factor VII in cardiac surgery. *Blood Coagul Fibrinolysis (Suppl 1)*:S31-S32, 2004
- Ferguson TB Jr, Hammill BG, Peterson ED, et al: A decade of change—risk profiles and outcomes for isolated coronary artery bypass grafting procedures, 1990-1999: A report from the STS National Database Committee and the Duke Clinical Research Institute. *Society of Thoracic Surgeons. Ann Thorac Surg* 73:480-489, 2002
- Landoni G, Rodseth RN, Santini F, et al: Randomized evidence for reduction of perioperative mortality. *J Cardiothorac Vasc Anesth* 26:764-772, 2012
- Oliveira MA, Brandi AC, Santos CA, et al: Modes of induced cardiac arrest: Hyperkalemia and hypocalcemia—literature review. *Rev Bras Cir Cardiovasc* 29:432-436, 2014
- DiNardo JA, Zvara DA: Myocardial preservation during cardiopulmonary bypass. In DiNardo JA, Zvara DA eds: *Anesthesia for cardiac surgery* ed. Oxford, UK, Blackwell Publishing, 2008, pp. 409-424
- Warltier DC, Pagel PS, Kersten JR: Approaches to the prevention of perioperative myocardial ischemia. *Anesthesiology* 92:253-259, 2000
- Cason BA, Gamperl AK, Slocum RE, et al: Anesthetic-induced preconditioning: Previous administration of isoflurane decreases myocardial infarct size in rabbits. *Anesthesiology* 87:1182-1190, 1997
- 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* 1:34-43, 2009
- Soro M, Gallego L, Silva V, et al: Cardioprotective effect of sevoflurane and propofol during anaesthesia and the postoperative period in coronary bypass graft surgery: A double-blind randomised study. *Eur J Anaesthesiol* 29:561-569, 2012
- 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
- 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

12. Julier K, da Silva R, Garcia C, et al: 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* 98:1315-1327, 2003
13. 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
14. 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
15. De Hert SG, Van der Linden PJ, Cromheecke S, et al: 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
16. Guarracino F, Landoni G, Tritapepe L, et al: Myocardial damage prevented by volatile anesthetics: A multicenter randomized controlled study. *J Cardiothorac Vasc Anesth* 20:477-483, 2006
17. Pagel PS: Myocardial protection by volatile anesthetics in patients undergoing cardiac surgery: a critical review of the laboratory and clinical evidence. *J Cardiothorac Vasc Anesth* 27:972-982, 2013
18. Kunst G, Klein AA: Peri-operative anaesthetic myocardial preconditioning and protection - cellular mechanisms and clinical relevance in cardiac anaesthesia. *Anaesthesia* 70:467-482, 2015
19. Bignami E, Landoni G, Gerli C, et al: Sevoflurane vs. propofol in patients with coronary disease undergoing mitral surgery: A randomised study. *Acta Anaesthesiol Scand* 56:482-490, 2012
20. 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
21. 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
22. Yao YT, Li LH: 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* 24:133-141, 2009
23. Landoni G, Greco T, Biondi-Zoccai G, et al: Anaesthetic drugs and survival: A Bayesian network meta-analysis of randomized trials in cardiac surgery. *Br J Anaesth* 111:886-896, 2013
24. Landoni G, Biondi-Zoccai GG, 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
25. Kohro S, Hogan QH, Nakae Y, et al: Anesthetic effects on mitochondrial ATP-sensitive K channel 1435-340. *Anesthesiology* 95:1435-1440, 2001
26. Borisov KY, Moroz VV, Grebenchikov OA, et al: Effect of propofol on sevoflurane-induced myocardial preconditioning in the experiment. *Gen Reanimatol* IX:30-35, 2013
27. Pasin L, Landoni G, Cabrini L, et al: Propofol and survival: A meta-analysis of randomized clinical trials. *Acta Anaesthesiol Scand* 59:17-24, 2015
28. Tritapepe L, Landoni G, Guarracino F, et al: Cardiac protection by volatile anaesthetics: A multicentre randomized controlled study in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass. *Eur J Anaesthesiol* 24:323-331, 2007
29. Garcia C, Julier K, Bestmann L, et al: Preconditioning with sevoflurane decreases PECAM-1 expression and improves one-year cardiovascular outcome in coronary artery bypass graft surgery. *Br J Anaesth* 94:159-165, 2005
30. Nozohoor S, Nilsson J, Algotsson L, et al: Postoperative increase in B-type natriuretic peptide levels predicts adverse outcome after cardiac surgery. *J Cardiothorac Vasc Anesth* 25:469-475, 2011
31. Nigro Neto C, Costa E, Rossi R, et al: Inhalation induction with sevoflurane in adult cardiac surgery patients. A case series. *Heart Lung Vessel* 6:8-12, 2014
32. Thielmann M, Kottenberg E, Kleinbongard P, et al: Cardioprotective and prognostic effects of remote ischaemic preconditioning in patients undergoing coronary artery bypass surgery: A single-centre randomised, double-blind, controlled trial. *Lancet* 382:597-604, 2013
33. Zarbock A, Schmidt C, Van Aken H, et al: Effect of remote ischemic preconditioning on kidney injury among high-risk patients undergoing cardiac surgery: A randomized clinical trial. *JAMA* 313:2133-2141, 2015
34. Zangrillo A, Musu M, Greco T, et al: Additive effect on survival of anaesthetic cardiac protection and remote ischemic preconditioning in cardiac surgery: A Bayesian network meta-analysis of randomized trials. *PLoS One* 10:e0134264, 2015
35. Hausenloy DJ, Candilio L, Evans R, et al: Remote ischemic preconditioning and outcomes of cardiac surgery. *N Engl J Med* 373:1408-1417, 2015
36. Meybohm P, Bein B, Brosteanu O, et al: A multicenter trial of remote ischemic preconditioning for heart surgery. *N Engl J Med* 373:1397-1407, 2015
37. Landoni G, Baiardo Redaelli M, Votta CD: Remote ischemic preconditioning and cardiac surgery. *N Engl J Med* 374:489, 2016
38. Bein B, Renner J, Caliebe D, et al: The effects of interrupted or continuous administration of sevoflurane on preconditioning before cardio-pulmonary bypass in coronary artery surgery: Comparison with continuous propofol. *Anaesthesia* 63:1046-1055, 2008
39. Jovic M, Stancic A, Nenadic D, et al: Mitochondrial molecular basis of sevoflurane and propofol cardioprotection in patients undergoing aortic valve replacement with cardiopulmonary bypass. *Cell Physiol Biochem* 29:131-142, 2012
40. Huang Z, Zhong X, Irwin MG, et al: Synergy of isoflurane preconditioning and propofol postconditioning reduces myocardial reperfusion injury in patients. *ClinSci (Lond)* 121:57-69, 2011