The Heart Surgery Forum #2008-1137
12 (1), 2009 [Epub February 2009]
doi: 10.1532/HSF98.20081137

Online address: http://cardenjennings.metapress.com

Cardioprotective Effects of Sevoflurane, Isoflurane, and Propofol in Coronary Surgery Patients: A Randomized Controlled Study

Vedat Yildirim,[1] Suat Doganci,[2] Ahmet Aydin,[3] Cengiz Bolcal,[2] Ufuk Demirkilic,[2] Ahmet Cosar[1]

Departments of [1]Anesthesiology and Reanimation, [2]Cardiovascular Surgery, and 3Pharmaceutical Toxicology, Gulhane Military Academy of Medicine, Ankara, Turkey

ABSTRACT

Background: This study was undertaken to compare the in vivo effects of isoflurane, sevoflurane, and propofol anesthesia on ischemia- and reperfusion-mediated free-radical injury and oxidative stress during coronary arety bypass graft surgery. We also compared the effects of these anesthetic agents on levels of end products of lipid peroxidation and nitric oxide (NO) in human right atrial tissue and blood.

Methods: Sixty patients scheduled to undergo elective coronary surgery with cardiopulmonary bypass (CPB) were enrolled. Patients were randomly allocated to receive 1 of 3 different anesthetic protocols: propofol (group A), isoflurane (group B), or sevoflurane (group C). We recorded global hemodynamic data (mean arterial pressure, mean pulmonary artery pressure, central venous pressure, pulmonary capillary wedge pressure, cardiac output, cardiac index, and systemic vascular resistance index) just before the start of surgery, before the start of CPB, 15 minutes after the end of CPB, at the end of the operation, 6 hours after installation in the intensive care unit, and 12 and 24 hours later. Samples of the right atrial appendage were harvested before and after exposure of the heart to blood cardioplegia and short-term reperfusion under conditions of CPB. Biochemical and oxidative stress parameters were analyzed in both blood and tissue.

Results: Hemodynamic parameters were kept stable throughout in all groups. Troponin I increased transiently with all used anesthetic regimens, but this increase was significantly lower in groups B and C. After clamp removal, lipid peroxidation in patients who received propofol (group A) was less than in patients who received isoflurane (group B) or sevoflurane (group C) ($P = .001$, $P = .005$, respectively). Although the 3 groups showed no statistically significant differences in tissue levels of thiobarbituric acid–reactive substances and superoxide dismutase, propofol significantly lowered NO production in atrial tissue after clamp removal and induced less NO production than sevoflurane ($P < .05$).

Conclusion: Inhalation anesthetics such as isoflurane and sevoflurane preserved cardiac function in coronary surgery patients after CPB with less evidence for myocardial damage than propofol. Furthermore, propofol induced lower blood levels of lipid peroxidation than isoflurane and sevoflurane. Propofol also increased glutathione peroxidase activity but induced less NO production compared to sevoflurane. These findings also support the cardioprotective properties that are demonstrated by hemodynamic parameters.

Received November 15, 2008; accepted January 7, 2009.

Correspondence: Vedat Yildirim, GATA Kalp Damar Cerrahi AD. 06018, Etlik/Ankara, Turkey; +90 312 3045218; fax: +90 312 3227898; (e-mail: drvyildirim@yahoo.com).

INTRODUCTION

Myocardial dysfunction after coronary bypass surgery is a well-known phenomenon that may significantly affect postoperative prognosis [Berger 1981]. Not only surgical revascularization but also the effectiveness of myocardial preservation determine the maintenance of ventricular function and thus the postoperative outcome. The extent of coronary artery disease, the degree of left ventricular dysfunction, and older age were reported to be among the most important determinants for postoperative myocardial dysfunction and morbidity and mortality after coronary surgery [De Hert 2003; De Hert 2004a; De Hert 2004b; Guarracino 2006; Jakobsen 2007; Landoni 2007; Tritapepe 2007].

Experimental data have indicated that anesthetic agents may exert cardioprotective effects that are independent of coronary blood flow or the reduction in cardiac work. The inability to relate these effects of volatile anesthetics to an improvement of the myocardial oxygen supply-demand balance has led to the concept that these agents may have direct cardioprotective effects [Kersten 1996; Hanouz 2002].

Although the available data on volatile anesthetics seem rather straightforward, the data on possible cardioprotective effects of propofol seem more controversial. Propofol may enhance antioxidant capacity, and this property has been claimed to protect the myocardium. The possible implications of this increase in antioxidant capacity for preservation of tissue function, however, remain to be demonstrated [Murphy 1992].

Propofol, which is a scavenger of free oxygen radicals, has a chemical structure resembling that of phenol-based antioxidants [Ansley 1999]. Studies have found oxygen free radicals in many different tissues after reperfusion. Sayin et al [2002]

demonstrated that propofol strongly attenuated lipid peroxidation during coronary artery bypass graft (CABG) surgery. Lipid peroxides and hydroperoxides, which cause increased cell membrane permeability resulting in disruption of the membrane, are formed during the reaction of free radicals with fatty acids of cell membranes [Ytrehus 1991]. Free radicals have also been shown to have deleterious effects on myocardium during reperfusion [Becker 2004].

Some unclear points remain to be clarified in the antioxidant and antiinflammatory processes associated with anesthetics. We sought to elucidate these points by comparing the in vivo effects of isoflurane, sevoflurane, and propofol anesthesia on ischemia- and reperfusion-mediated free radical injury and oxidative stress during CABG surgery and to compare the effects of these anesthetic agents on levels of end products of lipid peroxidation and nitric oxide (NO) in human right atrial tissue and blood.

MATERIALS AND METHODS

Patient Population

The study was approved by the ınstitutional ethical committee, and written informed consent was obtained from all patients. Sixty patients scheduled to undergo elective coronary surgery with cardiopulmonary bypass (CPB) were enrolled. Exclusion criteria were previous coronary or valvular heart surgery, combined surgical procedures (simultaneous valve repair, carotid endarterectomy, or left ventricle aneurysm repair), unstable angina, valve insufficiency, documented myocardial infarction within the previous 6 weeks, active congestive heart failure, hemodynamic instability requiring medical or mechanical support, severe hepatic disease (alanine amino transferase or aspartate amino transferase 150 U/L), renal insufficiency (creatinine concentration >1.5 mg/dL), severe chronic obstructive pulmonary disease (forced expired volume in 1 second 50% of predicted or 2.0 L), or history of neurological disturbances.

Study Groups

Patients were randomly allocated to receive 1 of 3 different anesthetic protocols: propofol (group A), isoflurane (group B), or sevoflurane (group C) anesthesia. A computer-generated random code was used to determine which anesthetic protocol was identified by each treatment number. Subjects were assigned the treatment numbers in ascending chronological order of admission in the study. The participant randomization assignment was concealed in an envelope until the start of anesthesia. The surgeons, research assistants, and medical and nursing staff in the intensive care unit (ICU) and on the ward were blinded to the group assignments.

Anesthesia and Surgery

All preoperative cardiac medications except angiotensin-converting enzyme inhibitors and angiotensin II antagonists were continued until the morning of surgery. Premedication was standardized for all patients, with 10 mg diazepam (Nervium®, Saba AS, Istanbul, Turkey) given orally 60 minutes before the surgery. In the operating room patients received routine monitoring, including 5-lead electrocardiogram, radial and pulmonary artery catheters with continuous cardiac output measurement (Swan Ganz CCO/VIP; Edwards Lifesciences, Irvine, Canada), pulse oxymetry, capnography, and blood and urine bladder temperature monitoring. In all patients, bispectral index monitoring (BIS A2000 system; Aspect Medical Systems, Newton, MA, USA) was applied. Concentration of anesthetic agents in all groups was titrated to maintain a bispectral index value of less than 50 throughout the procedure.

Patients were allocated to receive either a complete intravenous anesthetic regimen, based on propofol (Propofol®; Fresenius Kabi, Bad Homburg, Germany), or an inhalational anesthetic regimen, based on sevoflurane (Sevorane®; Abbott, Queenbrouugh, UK), or isoflurane (Forane®; Abbott). In all groups, a continuous infusion of remifentanil (Ultiva®; Glaxo-SmithKline, Genval, Belgium) was administered throughout the operation. Muscle relaxation was obtained with 0.1 mg/kg vecuronium bromide (Norcuron®; Organon, Oss, Holland).

In group A (n = 20), anesthesia was induced with a 1µg/kg bolus of remifentanil followed by a continuous infusion of 0.4 µg/kg per minute and a target-controlled infusion of propofol at 2 µg/mL. In group B (n = 20), anesthesia was induced with a 1 µg/kg bolus of remifentanil combined with midazolam (Dormicum®; Roche, Gaillard, France) 0.1 mg/kg, followed by a continuous infusion of 0.4 µg/kg per minute remifentanil. In group C (n = 20), anesthesia was induced with a 1µg/kg bolus of remifentanil followed by a continuous infusion of 0.4 µg/kg per minute, sevoflurane was initially started at 8%, and when the patient was asleep, it was lowered to a concentration of 2%.

In group A, anesthesia was maintained with 0.3-0.6 µg/kg per minute remifentanil and 2-4 mg/mL target-controlled infusion propofol. In group B, anesthesia was maintained with 0.3-0.6 µg/kg per minute remifentanil and 0.5%-1% isoflurane. In group C, anesthesia was maintained with 0.3-0.6 µg/kg per minute remifentanil and 0.5%-2% sevoflourane.

Routine cardioprotective strategies were used in all patients. These included the intravenous administration of 2 g methylprednisolone after induction of anesthesia.

Standard median sternotomy and pericardiotomy were performed. After administration of 300 U/kg heparin, the aortic cannula was secured in place. Activated coagulation time was kept above 450 seconds throughout the CPB period. St. Thomas II cardioplegia solution was used for diastolic cardiac arrest. Systemic temperature was allowed to drift during CPB to 28°C. Hematocrit concentrations were maintained between 20% and 25%, and on CPB (Roller pump [Sarns Perfusion System 9000; Baxter Healthecare, Ann Arbor, MI USA] and membrane oxygenators [Dideco 41037 Mirandola Italy]), a nonpulsatile flow was maintained between 2.2 and 2.5 L/min per m^2. The mean perfusion pressure was kept at 50-60 mmHg.

Before and after CPB, 2 right atrial samples were obtained from all patients, as described below. During CPB, anesthesia was maintained in group A with remifentanil and target-controlled propofol infusion; in group B with remifentanil and isoflurane; and in group C with remifentanil and sevoflurane. After the surgical procedure, reperfusion of the heart (reperfusion time was set at 50% of the aortic

cross-clamp time in all patients) and rewarming to a bladder temperature of 35°C. When the cardiac index was below 2.5 L/min per m^2, dobutamine was initiated. When mean arterial pressure was below 60 mmHg, vasoconstrictive therapy with phenylephrine was started.

Table 1. Patient Characteristics*

	Propofol (n = 20)	Isoflurane (n = 20)	Sevoflurane (n = 20)
Preoperative data			
Sex, M/F	14/6	15/5	16/4
Age, y	67 ± 10	69 ± 9	68 ± 11
Length, cm	171 ± 8	174 ± 7	169 ± 9
Weight, kg	81 ± 13	77 ± 11	79 ± 12
BSA, m2	1.92 ± 0.19	1.91 ± 0.18	1.89 ± 0.19
EF, %	45 ± 4	46 ± 5	42 ± 4
Previous myocardial infarction	5	6	5
Diabetes	5	7	6
COPD	2	3	2
Medication			
β-blockers	17	16	18
Calcium channel blockers	17	16	18
ACE inhibitors	5	5	5
Nitrates	6	5	7
Diuretics	17	15	15
Antiarrhythmic agents	7	8	8
Platelet aggregation inhibitors	0	0	0
Intraoperative data			
No. bypasses	18	18	17
No. arterial grafts	3 (3-6)	4(2-5)	3 (3-6)
Cross-clamp time, min	2 (1-3)	2 (1-3)	2 (1-3)
CPB time, min	40 ± 12	39 ± 19	36 ± 15
Duration	114 ± 38	109 ± 23	106 ± 26
Anesthesia, min	324 ± 89	345 ± 79	333 ± 94
Surgery, min	221 ± 82	237 ± 76	241 ± 64
Postoperative data			
Mechanical ventilation, h	4.8 ± 0.7	3.6 ± 0.5	3.4 ± 0.5
Prolonged mechanical ventilation (>12 h), n (%)	4(20)*	2(10)	1(5)
ICU stay, h (min-max)	20 (17-24)	19 (17-24)	19 (17-24)
Prolonged hospitalization (>7 d), n (%)	7(35)†	3(15)	2(10)
Death at 30 days, n	0	0	0

*Data are n, mean ± SD), or median (range). BSA, body surface area; EF, ejection fraction; ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; ICU, intensive care unit.

†$P < .05$.

After a stabilization period of 15 minutes to allow for recovery of systolic and diastolic data after CPB, the post-CPB measurements were obtained. After CPB, anesthesia was maintained with remifentanil combined with propofol in group A, isoflurane in group B, and sevoflurane in group C.

After removal of the aortic cannula, heparin activity was neutralized with protamine at a ratio of 1 mg protamine for 100 U heparin. Protamine administration was further guided by activated coagulation time measurements, aiming at a value of 140 seconds. At the end of the surgical procedure, patients were transferred to the ICU.

Hemodynamic Data Analysis

Global hemodynamic data (mean arterial pressure, mean pulmonary artery pressure, central venous pressure, pulmonary capillary wedge pressure, cardiac output, cardiac index, and systemic vascular resistance index) were registered just before the start of surgery (base), before the start of CPB (pre-CPB), 15 minutes after the end of CPB (post-CPB), at the end of the operation, 6 hours after installation in the ICU (ICU 6), and 12 hours (ICU 12) and 24 hours (ICU 24) later.

Tissue Harvesting

Samples of the right atrial appendage were harvested from all patients (n = 60) before and after exposure of the heart to cardioplegia and short-term reperfusion under conditions of CPB. Samples were harvested with cold sharp dissection and handled in a nontraumatic fashion. Double 3-0 polypropylene purse-string sutures (Ethicon) were placed in the atrial appendage. During placement of the venous cannula, the first sample of atrial appendage was harvested. The superior suture was tightened to secure the venous cannula. The inferior suture remained loose to allow this portion of the atrium to be perfused with blood, exposed to CPB and cardioplegia, and reperfused after removal of the aortic cross-clamp. The second sample of atrial appendage was harvested after cold blood cardioplegia/CPB during removal of the venous cannula. Myocardial tissue was immediately frozen in liquid nitrogen for molecular biology studies.

Biochemical Analysis

In all patients, blood was sampled for determination of cardiac troponin I. These samples were obtained before the induction of anesthesia (base), at arrival in the ICU (end of surgery), and at ICU 6, ICU 12, ICU 24, and 48 hours later (ICU 48). Sensitivity of cardiac troponin I determination in the institutional laboratory is 0.04 ng/mL. The cutoff value for severe myocardial damage was determined as 2 ng/mL [De Hert 2004b].

Pharmacological Analysis

Pharmacolgical analyses included determination of oxidative stress parameters and NO measurement. We used spectrometric methods to determine thiobarbituric acid–reactive substance (TBARS) levels and superoxide dismutase (CuZn-SOD) and glutathione peroxidase (GPX) activities in the erythrocyte lysate at preinduction, before cannulation, after

clamp removal, and 24 hours after CABG. CuZn-SOD and GPX activities in myocardial tissue homogenate along with TBARS levels and NO were determined in the right atrial appendage before cannulation and after clamp removal.

After patients had fasted overnight, blood samples were drawn from the antecubital vein by venopuncture into tubes containing EDTA. Each blood sample was centrifuged at 4000*g* for 10 minutes at 4°C. After removal of plasma and buffy coats, erythrocytes were washed 3 times with 3 volumes of isotonic saline. Erythrocytes were then lysed with cold distilled water (1:4) and stored in a refrigerator at 4°C for 15 minutes, and then cell debris was removed by centrifugation (2000*g* for 10 minutes). Plasma samples and erythrocyte lysates were stored at –70°C until assayed.

Tissue samples were homogenized in 1.5% KCl solution on ice using a glass homogenizer. Then homogenized samples were centrifuged for 10 minutes at 5000*g* and 4°C. Supernatant was used for the analysis.

All oxidative stress measurements were done according to our previous studies [Bolcal 2007; Aydin 2001].

Statistical Analysis

To compare patient characteristics we used Fisher exact test and a 1-way ANOVA as appropriate. Medians were compared with the Kruskal-Wallis 1-way ANOVA test on ranks. Data before and after CPB were compared using an ANOVA for repeated measurements. Interaction analysis revealed whether effects were different among groups. Posttest analysis was performed using the Bonferroni-Dunn test. Because values of troponin I do not have a gaussian distribution, the data were expressed as median and the 95% confidence interval. Statistical significance was accepted at $P < .05$. All P values were 2-tailed. SPSS version 15.0 was used to perform statistical analyses.

RESULTS

There were no significant differences in patient characteristics, which are summarized in Table 1. Complete revascularization was performed, and surgery was uneventful in all patients. Bispectral index monitoring values were similar in all groups. None of the patients developed myocardial infarction perioperatively.

Mean arterial pressure, mean pulmonary artery pressure, central venous pressure, and systemic vascular resistance index were kept stable throughout in all groups. After CPB and at the end of the operatio, and at ICU 6, cardiac output and

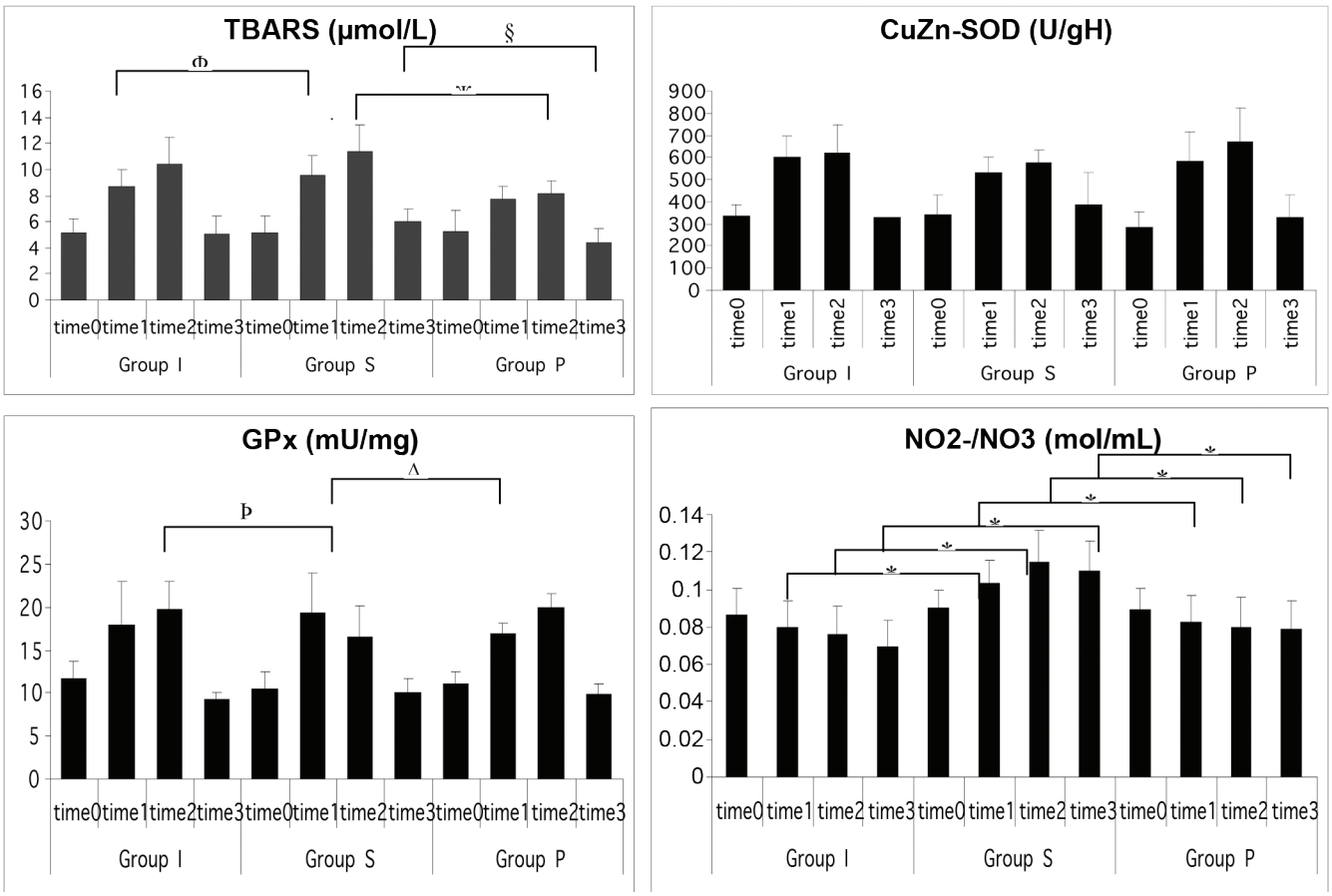

Figure 1. Blood oxidative stress status and nitric oxide levels after reperfusion injury. Group I, isoflourane group; Group S, sevoflurane group; Group P, propofol group; time0; preinduction; time1, before cannulation; time2, after clamp removal; time3, 24 hours after coronary artery bypass graft; TBARS, thiobarbituric acid reactive substances; Cu-Zn SOD, superoxide dismutase; GPx, glutathion peroxidase; NO2/NO3, nitrite/nitrate; *$P < .05$; Φ$P = .005$; Ж$P = .001$; §$P = .004$; Δ$P = .018$; Þ$P = .020$.

Table 2. Pre- and Postoperative Hemodynamic Data

	Base	Pre-CPB	Post-CPB	End of the operation	ICU 6	ICU 12	ICU 24
HR, beats/min							
Propofol (n = 20)	71 ± 11	74 ± 15	58 ± 42	73 ± 12	76 ± 14	80 ± 11	84 ± 13
Isoflurane (n = 20)	73 ± 12	76 ± 13	64 ± 39	80 ± 15	84 ± 10	83 ± 8	82 ± 9
Sevoflurane (n = 20)	70 ± 14	74 ± 10	60 ± 37	78 ± 13	81 ± 9	79 ± 10	86 ± 12
MAP, mmHg							
Propofol	72 ± 10	76 ± 10	72 ± 11	74 ± 7	74 ± 10	75 ± 10	81 ± 7
Isoflurane	73 ± 12	76 ± 7	70 ± 8	79 ± 11	76 ± 9	81 ± 12	78 ± 14
Sevoflurane	71 ± 9	75 ± 9	73 ± 9	77 ± 8	75 ± 8	77 ± 11	83 ± 8
MPAP, mmHg							
Propofol	22 ± 3	21 ± 2	23 ± 2	23 ± 2	22 ± 4	22 ± 2	20 ± 3
Isoflurane	23 ± 3	24 ± 3	23 ± 3	24 ± 3	23 ± 2	23 ± 2	23 ± 4
Sevoflurane	22 ± 2	21 ± 3	22 ± 3	24 ± 2	22 ± 2	21 ± 3	24 ± 3
CVP, mmHg							
Propofol	11 ± 3	13 ± 3	12 ± 3	11 ± 3	11 ± 4	12 ± 2	11 ± 3
Isoflurane	13 ± 3	12 ± 3	13 ± 3	13 ± 2	13 ± 4	11 ± 3	13 ± 3
Sevoflurane	12 ± 3	11 ± 3	11 ± 3	12 ± 2	11 ± 3	12 ± 3	12 ± 3
PCWP, mmHg							
Propofol	14 ± 3	13 ± 3	14 ± 3	11 ± 3	13 ± 3	12 ± 2	14 ± 3
Isoflurane	14 ± 2	14 ± 3	15 ± 3	13 ± 3	12 ± 3	11 ± 3	15 ± 3
Sevoflurane	13 ± 3	14 ± 2	13 ± 4	12 ± 3	13 ± 3	12 ± 3	15 ± 3
CO, L/min							
Propofol	5.8 ± 1.1	5.4 ± 0.9	4.5 ± 0.8†‡	4.7 ± 0.4‡	4.6 ± 0.4†‡	5.2 ± 0.7	5.1 ± 0.7
Isoflurane	5.2 ± 0.7	4.9 ± 0.8	5.5 ± 0.6‡	5.6 ± 0.5‡	5.6 ± 0.5‡	5.4 ± 0.9	5.6 ± 0.6
Sevoflurane	5.3 ± 0.7	5.5 ± 0.9	5.3 ± 0.7	5.4 ± 0.5	5.4 ± 0.7	5.5 ± 0.5	5.3 ± 0.7
CI, L/min per m2							
Propofol	2.5 ± 0.5	2.4 ± 0.5	2.0 ± 0.4†	2.1 ± 0.4†	2.2 ± 0.4†	2.5 ± 0.5	2.6 ± 0.6
Isoflurane	2.4 ± 0.5	2.5 ± 0.6	2.5 ± 0.5	2.7 ± 0.2	2.8 ± 0.4	2.7 ± 0.6	2.7 ± 0.5
Sevoflurane	2.5 ± 0.5	2.4 ± 0.6	2.6 ± 0.3	2.8 ± 0.3	2.7 ± 0.4	2.7 ± 0.6	2.8 ± 0.4
SVRI, dyne/s per cm5 per m2							
Propofol	1765 ± 398	1813 ± 408	1847 ± 346	1846 ± 293	1784 ± 341	1809 ± 361	1810 ± 331
Isoflurane	1773 ± 392	1784 ± 293	1792 ± 314	1830 ± 350	1787 ± 338	1792 ± 311	1798 ± 293
Sevoflurane	1821 ± 347	1804 ± 343	1770 ± 285	1740 ± 380	1785 ± 329	1769 ± 332	1796 ± 271

*CPB, cardiopulmonary bypass; HR, heart rate; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; CI, cardiac index; SVRI, systemic vascular resistance index.

†Different compared with base.

‡Different compared with other groups.

cardiac index were significantly lower in the propofol group, whereas they remained stable in the isoflurane group and sevoflurane group. From time point ICU 12, the transient decrease in cardiac output and cardiac index in the propofol group returned to normal levels (Table 2).

All patients were successfully weaned from CPB. Post-CPB, there were no significant differences in the use of inotropic therapy (5 patients in group A, 4 in group B, and 4 in group C) or vasoconstrictive therapy (6 patients in group A, 5 in group B, and 5 in group C). In the ICU, the need for inotropic support was similar in all groups (6 patients in group A, 6 in group B, and 5 in group C). The need for vasoconstrictive therapy in the ICU was also similar in the 3 groups (8 patients in group A, 7 in group B, and 7 in group C).

The arterial blood gas values and hemoglobin concentrations at the different times were similar in all groups.

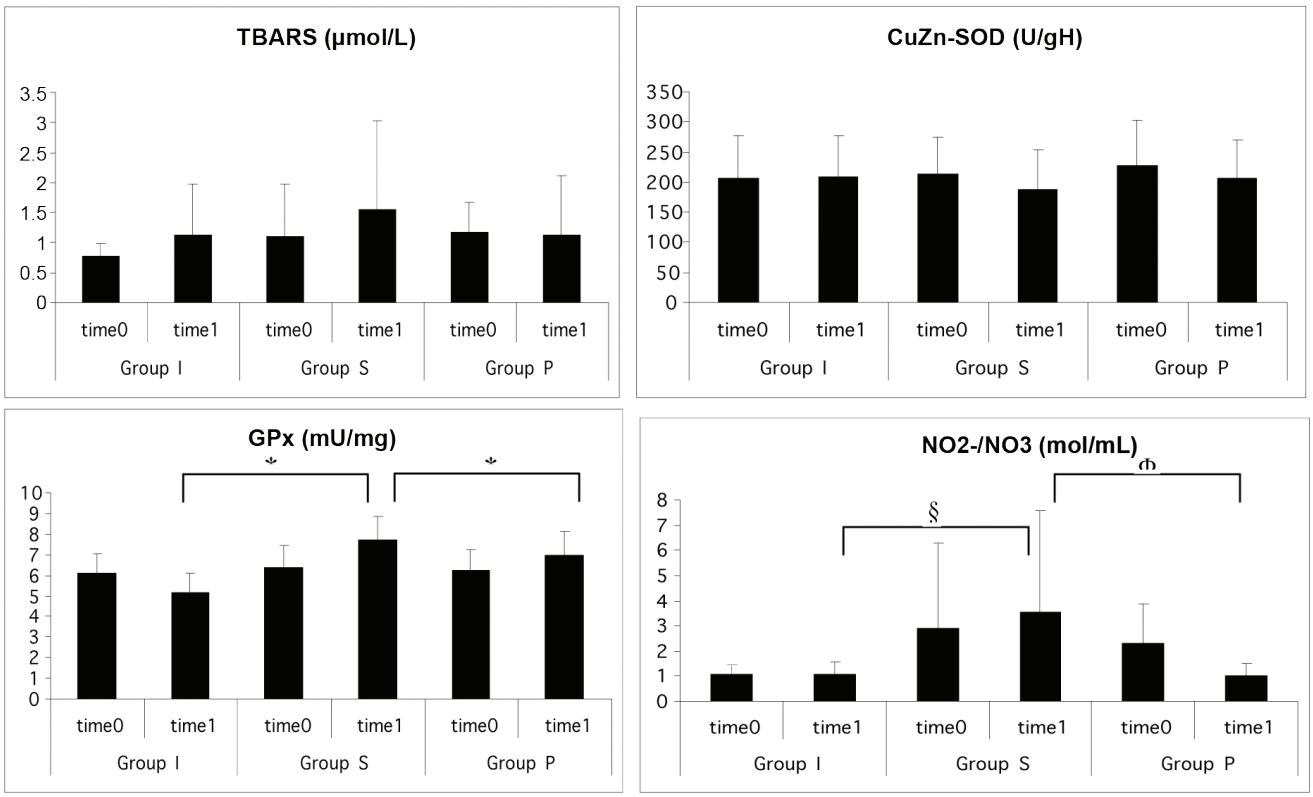

Figure 2. Myocardial oxidative stress status and nitric oxide levels after reperfusion injury. Group I, isoflourane group; Group S, sevoflurane group; Group P, propofol group; time1, before cannulation; time2, after clamp removal; TBARS, thiobarbituric acid reactive substances; Cu-Zn SOD, superoxide dismutase; GPx, glutathion peroxidase; NO2/NO3, nitrite/nitrate; *P < .05; §P = .029; ΦP = .027.

Troponin I values were similar in all groups at base (before induction of anesthesia) measurement. Troponin I increased transiently with all used anesthetic regimens, but this increase was significantly lower in the groups B and C. The incidence of important myocardial damage (defined as a postoperative troponin I >2 ng/mL) was also significantly lower in the isoflurane and sevoflurane groups. For groups B and C troponin I concentrations remained below the cutoff value throughout the observation period. In group A, on the contrary, elevation in troponin I concentrations was observed at end of surgery, with peaks at ICU 6, ICU 12, and ICU 24 followed by a decreased at ICU 48 (Table 3).

Lipid peroxidation was lower in the propofol group than in the isoflurane and sevoflurane groups after clamp removal (P = .001 and P = .005, respectively). Free radical formation before cannulation, after clamp removal, and 24 hours after the CABG procedure was also higher in the propofol group compared to the sevoflurane group (P = .005, P = .001, and P = .004, respectively). CuZn-SOD activities tended to increase in all groups during the venous sampling periods, but the difference did not reach statistical significance (P > .05). GPX activity was higher in the propofol and isoflurane groups compared to the sevoflurane group after clamp removal (Figure 1).

Although the 3 groups showed no statistically significant differences in tissue TBARS and SOD levels, patients in the propofol group had significantly lower NO production in the atrial tissue after clamp removal and less NO production than patients in the sevoflurane group (P < .05) (Figure 2).

DISCUSSION

Our results indicate that the choice of the anesthetic regimen influences postoperative myocardial function and the extent of myocardial damage in coronary surgery patients. The patients who were anesthetized with sevoflurane and isoflurane had significantly better function, lower postoperative troponin I levels, and less need for inotropic support than the patients anesthetized with propofol.

Demographic data, number of grafts, type of cardioprotection, aortic cross-clamp time, and CPB were similar in all patients, which suggest that the differences in cardiac function between the groups were not caused by differences in patient characteristics and intraoperative events but instead seem to be related to the choice of anesthetic agent.

The underlying mechanisms responsible for the differences in postoperative cardiac function and extent of myocardial damage in these patients cannot be elucidated from the study. It is impossible in the presence of an unknown and unquantified decrement in cardiac function related to coronary surgery to distinguish between a potential cardioprotective effect of the volatile anesthetics or a possible negative effect of the total intravenous anesthetic regimen on myocardial function.

Experimental observations have repeatedly demonstrated a cardioprotective effect of volatile anesthetics [Kersten 1996; Hanouz 2002]. Whereas the available data on volatile anesthetics seem rather straightforward, the data on possible cardioprotective effects of propofol seem more controversial. Propofol may enhance antioxidant capacity, and this property has been suggested to protect the myocardium [Kokita 1996]. The possible implications of this increase in antioxidant capacity for preservation of tissue function, however, remain to be investigated.

Our study showed that propofol was superior to isoflurane and sevoflurane in terms of lipid peroxidation, although there were no significant differences at the tissue level. Protective effects of anesthetic agents on the myocardium remain speculative. Inhalation anesthetics were shown to afford protection against the deleterious consequences of myocardial ischemia-reperfusion injury [Kevin 2003]. Surprisingly, studies demonstrated that free radicals are essential mediators of cardioprotection [Baines 1997; Sommerschild 2002]. It was reported that the cardioprotective mechanism of isoflurane may be free-radical mediated. In a recent clinical trial, sevoflurane, but not propofol, was found to be cardioprotective [Mullenheim 2002; Jakobsen 2007]. Absence of this effect for propofol was related to its scavenging of free radicals [De Hert 2002; De Hert 2004a; De Hert 2004b; Tritapepe 2007]. The TBARS assay is a sophisticated method that provides an optimal lipid peroxide measurement [Lefevre 1998]. The cardioprotective effect of sevoflurane has been related to its radical scavenging properties [De Ruijter 2003].

Allaouchiche et al [2001] reported that propofol and sevoflurane were more likely to have antioxidant properties. In that study, consistent with our findings, no significant changes were found in circulating concentrations of SOD during exposure to propofol, sevoflurane, and desflurane.

Studies demonstrated that NO might play a critical role in cardioprotection against ischemia-reperfusion injury [Ding 2005]. Although sevoflurane increased NO production at the atrial tissue level, it did not reach statistical significance. In our study, surprisingly, propofol significantly lowered NO production in the atrial tissue after clamp removal.

The present study extends the observation that volatile anesthetics result in a better cardiac function and less evidence of myocardial damage, obtained in low-risk patients with good baseline cardiac function to a patient population that can be classified as high risk. The degree of dysfunction and the recovery pattern of myocardial function have been shown to be related to the preoperative ejection fraction. An ejection fraction greater than 55% was associated with moderate dysfunction immediately after CPB and almost completes recovery within 4 hours, whereas an ejection fraction less than 45% was associated with more severe dysfunction and a longer period of recovery [Mangano 1985]. This study allowed us to evaluate the effects of different anesthetic regimens in a patient population with documented impaired myocardial function, in which a transient postoperative myocardial dysfunction with need for inotropic support after CPB can be expected.

In the present study, anesthesia was in part based on a continuous infusion of remifentanil. However, dosages of remifentanil (and other drugs used in the present study) were similar in all groups, suggesting that the observed differences in cardiac function between both might be related to the choice between propofol, isoflurane, and sevoflurane. Another difference between the groups is the use of midazolam during induction of anesthesia in the isoflurane group. In this study, we aimed to limit the number of drugs used to clearly relate possible different effects to the anesthetics used. For propofol and sevoflurane, both induction and maintenance of anesthesia could be obtained with the same drug. However, induction of anesthesia with isoflurane is not possible. For this reason, induction of anesthesia in the patients in the isoflurane group was obtained with midazolam. It cannot be excluded that this may have contributed to the effects observed in isoflurane group. Effects of intravenous anesthetics on preservation of myocardial function are the subject of ongoing research. Recently, it was shown that the benzodiazepine midazolam had no effect on mitochondrial KATP channel activity in isolated adult rat cardiomyocytes, suggesting that no additional cardioprotection was to be expected with this type of drug [Zaugg 2002].

In all groups, a number of patients needed inotropic and vasoconstrictive support after CPB and in the first hours in the ICU. Obviously this treatment influenced the analysis of cardiac function in the different groups. The current data may therefore not be interpreted as net effects of propofol, isoflurane, or sevoflurane on cardiac function after CPB. However, the need for inotropic support was significantly higher in the propofol group, which provided an additional indication that isoflurane and sevoflurane better protected against myocardial dysfunction after CPB.

Cardiac troponin I is a sensitive marker for myocardial cellular damage [Etievent 1995; De Hert 2004a; De Hert 2004b]. Postoperative values of these enzymes were significantly lower in the isoflurane and sevoflurane groups than in the propofol group, which is consistent with a cardioprotective effect of these volatile anesthetics in the current clinical setting. Troponin I levels were increased with propofol, clearly above the cutoff value of 2 ng/mL and comparable to the value of

Table 3. Perioperative Troponin I Changes*

Parameters	Base	End of Surgery	ICU 6	ICU 12	ICU 24	ICU 48
Troponin I, ng/mL	0.50 ± 0.01	1.68 ± 0.65	2.91 ± 1.17	2.95 ± 1.42	2.60 ± 1.34	1.94 ± 0.86
Propofole	0.52 ± 0.01	0.64 ± 0.07	1.50 ± 0.79	1.46 ± 0.83	1.49 ± 1.04	1.28 ± 0.72
Isoflurane	0.51 ± 0.01	0.68 ± 0.06	1.67 ± 0.77	1.66 ± 0.79	1.58 ± 0.77	1.32 ± 0.67

*Blood samples were obtained before induction of anesthesia, at the end of surgery, and 6 h, 12 h, 24 h, and 48 h after arrival in the intensive care unit (ICU).

5.2 µg/L reported by Sadony et al [1998] in patients classified as having minor myocardial damage. Still, they compare favorable with the cutoff value of 13.4 µg/L reported by Jacquet et al [1998] to significantly separate patients with an uneventful recovery from those with myocardial ischemia and infarction. These results suggests that the choice of the anesthetic regimen similarly influences the extent of postoperative myocardial damage in coronary surgery patients with preserved and impaired preoperative myocardial function.

CONCLUSION

Ischemia-reperfusion injury has received considerable attention in the past decade because of its direct clinical relevance. Of importance to the anesthetists are several studies conducted on the effects of potent inhalation and intravenous anesthetics on ischemia-reperfusion injury. The results of the present study demonstrated that inhalation anesthetics such as isoflurane and sevoflurane preserved cardiac function in coronary surgery patients after CPB with less evidence for myocardial damage than with propofol. Furthermore, propofol induced less lipid peroxidation than both isoflurane and sevoflurane at the blood level. Propofol also increases GPX activity but induces less NO production compared to sevoflurane. These findings also support the cardioprotective properties that are demonstrated by hemodynamic parameters. Choosing a cardioprotective anesthetic regimen may help lower at least one risk, an advantage that ca not be underestimated considering its mitigation of a potentially fatal injury.

REFERENCES

Allaouchiche B, Debon R, Goudable J, et al. 2001. Oxidative stress status during exposure to propofol, sevoflurane and desflurane. Anesth Analg 93:981-5.

Ansley DM, Sun J, Visser WA, et al. 1999. High dose propofol enhances red cell antioxidant capacity during CPB in humans. Can J Anaesth 46:641-8.

Aydin A, Orhan H, Sayal A, Ozata M, Sahin G, Isimer A. 2001. Oxidative stress and nitric oxide related parameters in type II diabetes mellitus: effects of glycemic control. Clin Biochem 34:65-70.

Baines CP, Goto M, Downey JM. 1997. Oxygen radicals released during ischemic preconditioning contribute to cardioprotection in the rabbit myocardium. J Mol Cell Cardiol 29:207-16.

Becker LB. 2004. New concepts in reactive oxygen species and cardiovascular reperfusion physiology. Cardiovasc Res 61:461-70.

Berger RL, Davis KB, Kaiser GC, et al. 1981. Preservation of the myocardium during coronary artery bypass grafting. Circulation 64:II61-6

Bolcal C, Yildirim V, Doganci S, et al. 2007. Protective effects of antioxidant medications on limb ischemia reperfusion injury. J Surg Res 139:274-9.

De Hert SG, ten Broecke PW, Mertens E, et al. 2002. Sevoflurane but not propofol preserves myocardial function in coronary surgery patients. Anesthesiology 97:42-9.

De Hert SG, Cromheecke S, ten Broecke PW, et al. 2003. Effects of propofol, desflurane, and sevoflurane on recovery of myocardial function after coronary surgery in elderly high-risk patients. Anesthesiology 99:314-23.

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

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

De Ruijter W, Musters RJ, Boer C, et al. 2003. The cardioprotective effect of sevoflurane depends on protein kinase C activation, opening of mitochondrial K(+)(ATP) channels, and the production of reactive oxygen species. Anesth Analg 97:1370-6.

Ding HL, Zhu HF, Dong JW, et al. 2005. Inducible nitric oxide synthase contributes to intermittent hypoxia against ischemia/reperfusion injury. Acta Pharmacol Sin 26:315-22.

Etievent JP, Chocron S, Toubin G, et al. 1995. Use of cardiac troponin I as a marker of perioperative myocardial ischemia. Ann Thorac Surg May 59:1192-4.

Guarracino F, Landoni G, Tritapepe L, et al. 2006. Myocardial damage prevented by volatile anesthetics: a multicenter randomized controlled study. J Cardiothorac Vasc Anesth 20:477-83.

Hanouz JL, Yvon A, Massetti M, et al. 2002. Mechanisms of desflurane-induced preconditioning in isolated human right atria in vitro. Anesthesiology 97:33-41.

Jacquet L, Noirhomme P, El Khoury G, et al. 1998. Cardiac troponin I as an early marker of myocardial damage after coronary bypass surgery. Eur J Cardiothorac Surg 13:378-84.

Jakobsen CJ, Berg H, Hindsholm KB, Faddy N, Sloth E. 2007. The influence of propofol versus sevoflurane anesthesia on outcome in 10,535 cardiac surgical procedures. J Cardiothorac Vasc Anesth 21:664-71.

Kersten JR, Schmeling TJ, Hettrick DA, Pagel PS, Gross GJ, Warltier DC. 1996. Mechanism of myocardial protection by isoflurane. Role of adenosine triphosphate-regulated potassium (KATP) channels. Anesthesiology 85:794-807.

Kevin LG. 2003. Propofol and myocardial lipid peroxidation. Br J Anaesth 253:253-4.

Kokita N, Hara A. 1996. Propofol attenuates hydrogen peroxide-induced mechanical and metabolic derangements in the isolated rat heart. Anesthesiology 84:117-27.

Landoni G, Biondi-Zoccai GGL, Zangrillo A, et al. 2007. Desflurane and sevoflurane in cardiac surgery: a meta-analysis of randomised clinical trials. J Cardiothorac Vasc Anesth 21:502-11.

Lefevre G, Beljean-Leymarie M, et al. 1998. Evaluation of lipid peroxidation by measuring thiobarbituric acid reactive substances Ann Biol Ann Biol Clin (Paris) 56:305-19.

Mangano DT. 1985. Biventricular function after myocardial revascularization in humans: deterioration and recovery patterns during the first 24 hours. Anesthesiology 62:571-7.

Mullenheim J, Ebel D, Frabetadorf J, et al. 2002. Isoflurane preconditions myocardium against infarction via release of free radicals. Anesthesiology 96:934-40.

Murphy PG, Myers DS, Davies MJ, et al. 1992. The antioxidant potential of propofol (2,6-diisopropylphenol). Br J Anaesth 68:613-8.

Sadony V, Korber M, Albes G, et al. 1998. Cardiac troponin I plasma

levels for diagnosis and quantitation of perioperative myocardial damage in patients undergoing coronary artery bypass surgery. Eur J Cardiothorac Surg 13:57-65.

Sayın MM, Ozatamer O, Tasoz R, et al. 2002. Propofol attenuates myocardial lipid peroxidation during coronary artery bypass grafting surgery. Br J Anaesth 89: 242-6.

Sommerschild HT, Kirkeboen KA. 2002. Preconditioning-endogenous defence mechanisms of the heart. Acta Anaesthesiol Scand 46:123-37.

Tritapepe L, Landoni G, Guarracino F, et al. 2007. Cardiac protection by volatile anaesthetics: a multicentre randomized controlled study in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass. Eur J Anaesthesiol 24:323-31.

Ytrehus K, Hegstad AC. 1991. Lipid peroxidation and membrane damage of the heart. Acta Physiol Scand Suppl 599:81-91.

Zaugg M, Lucchinetti E, Spahn DR, Pasch T, Garcia C, Schaub MC. 2002. Differential effects of anesthetics on mitochondrial K(ATP) channel activity and cardiomyocyte protection. Anesthesiology 97:15-23.