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Sevoflurane but Not Propofol Preserves Myocardial Function in Coronary Surgery Patients

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Background: **Sevoflurane has been shown to protect against myocardial ischemia and reperfusion injury in animals. The present study investigated whether these effects were clinically relevant and would protect left ventricular (LV) function during coronary surgery.**

Methods: **Twenty coronary surgery patients were randomly assigned to receive either target-controlled infusion of propofol or inhalational anesthesia with sevoflurane. Except for this, anesthetic and surgical management was the same in all patients. A high-fidelity pressure catheter was positioned in the left ventricle and the left atrium. LV response to increased cardiac load, obtained by leg elevation, was assessed before and after cardiopulmonary bypass (CPB). Effects on contraction were evaluated by analysis of changes in dP/dt_{max}. Effects on relaxation were assessed by analysis of the load dependence of myocardial relaxation (R = slope of the relation between time constant τ of isovolumic relaxation and end-systolic pressure). Postoperative concentrations of cardiac troponin I were followed during 36 h.**

Results: **Before CPB, leg elevation slightly increased dP/dt_{max} in the sevoflurane group (5 ± 3%), whereas it remained unchanged in the propofol group (1 ± 6%). After CPB, leg elevation resulted in a decrease in dP/dt_{max} in the propofol group (−5 ± 4%), whereas the response in the sevoflurane group was comparable to the response before CPB (5 ± 4%). Load dependence of LV pressure fall (R) was similar in both groups before CPB. After CPB, R was increased in the propofol group but not in the sevoflurane group. Troponin I concentrations were significantly lower in the sevoflurane than in the propofol group.**

Conclusions: **Sevoflurane preserved LV function after CPB with less evidence of myocardial damage in the first 36 h postoperatively. These data suggest a cardioprotective effect of sevoflurane during coronary artery surgery.**

VOLATILE anesthetics have been shown to enhance recovery of contractile function of the stunned myocardium.[1–10] Sevoflurane mimics ischemic preconditioning with an improvement of postischemic contractility in isolated guinea pig hearts.[9] It also appears to reduce myocardial infarct size and to decrease the time threshold for ischemic preconditioning in dogs through activation of adenosine triphosphate–regulated potassium (K_{ATP}) channels.[10] More recently, it was observed in anesthetized dogs that sevoflurane had a cardioprotective effect that was mediated through activation of mitochondrial K_{ATP} channels. The cardioprotective effect was independent of coronary blood flow or the reduction in cardiac work.[11]

However, the clinical relevance of these experimental findings with volatile anesthetics have not previously been established. Two studies in coronary surgery patients have suggested a potential beneficial role for isoflurane in myocardial protection during the perioperative period. Belhomme *et al.*[12] observed consistently lower postoperative creatine kinase MB isoenzyme and troponin I concentrations, and Haroun-Bizri *et al.*[13] observed a higher cardiac index after coronary surgery in patients who were treated with isoflurane. Until now, no firm data on a potential beneficial role of sevoflurane in the preservation of cardiac function during coronary surgery were available. We hypothesized that if the reported cardioprotective effects of sevoflurane were clinically relevant, the use of sevoflurane would have beneficial effects on perioperative myocardial function and postoperative markers of myocardial tissue damage. To study this question, we compared two groups of coronary surgery patients in whom the only perioperative difference was the use of either sevoflurane or propofol in the anesthetic procedure. Baseline hemodynamic data, the ability of the ventricle to sustain increased load,[14,15] and postoperative markers of myocardial tissue damage (cardiac troponin I) were compared in both groups.

Methods

Patient Population

The study was performed in 20 patients scheduled for elective coronary bypass surgery. The study was approved by the Institutional Ethical Committee (University Hospital Antwerp, Edegem, Belgium), and written informed consent was obtained. Patients with a preoperative ejection fraction of more than 40% were included. Patients undergoing repeat coronary surgery, concurrent valve repair, or aneurysm resection were excluded. Patients with unstable angina or valve insufficiency were also excluded. None of the patients included in the present study had oral antidiabetic medication or were treated with theophylline. In all patients, acetylsalicylic acid was stopped for 1 week, and all patients received a daily dose of 0.6 ml nadroparine (5,700 IU anti-Xa) subcutaneously. Patients were randomly (by opening of an envelope) allocated to receive

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either propofol (group A) or sevoflurane (group B) anesthesia.

Anesthesia and Surgery

All preoperative cardiac medication was continued until the morning of surgery. In the operating room, patients received routine monitoring, including five-lead electrocardiography, radial and pulmonary artery catheters with continuous cardiac output measurement, pulse oximetry, capnography, and blood and urine bladder temperature monitoring. In group A, anesthesia was induced with a 1-μg/kg bolus of remifentanil followed by a continuous infusion of 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and a target-controlled infusion (TCI) of propofol at 2 mg/ml. In group B, anesthesia was induced with a 1-μg/kg bolus of remifentanil followed by a continuous infusion of 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$; sevoflurane was initially started at 8%, and when the patient was asleep, it was lowered to a concentration of 2%. In both groups, muscle paralysis was obtained with 0.1 mg/kg pancuronium bromide. In group A, anesthesia was maintained with 0.3–0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil and 2–4 mg/ml TCI propofol. In group B, anesthesia was maintained with 0.3–0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil and 0.5–2% sevoflurane. Standard median sternotomy and pericardiotomy were performed. After administration of 300 IU/kg heparin, the aortic canula was secured in place. Activated coagulation time (ACT) was kept above 450 s throughout the CPB period.

In each patient, two sterilized electronic tipmanometers (MTCP3Fc catheter; Dräger Medical Electronics, Best, The Netherlands; frequency response = 100 KHz) were set to zero and inserted. One catheter was positioned in the left atrium through the right superior pulmonary vein; the other catheter was positioned in the left ventricular (LV) cavity through the apical dimple. Both catheters were connected to a Hewlett Packard monitor (HP78342A; Hewlett Packard, Brussels, Belgium). The output signals of the pressure transducer system were digitally recorded together with the electrocardiographic signals at 1-ms intervals (Codas; DataQ, Akron, OH). Zero and gain settings of the tipmanometers were also checked against a high-fidelity pressure gauge (Druck Ltd., Leicester, United Kingdom) after removal.

Heart rate was kept constant by atrioventricular sequential pacing at a rate of 90 beats/min. All measurements were obtained with the ventilation suspended at end-expiration. The measurements consisted of recordings of consecutive electrocardiographic and LV pressure tracings during an increase of systolic and diastolic pressures obtained by raising the caudal part of the surgical table by 45°, resulting in raising of the legs. Leg elevation resulted in a rapid beat-to-beat increase in LV pressures.

A first set of measurements was obtained before cardiopulmonary bypass (CPB). After this measurement, the catheters were removed, the venous cannula was inserted, and CPB was initiated. Routine surgical technique and cardioprotective strategies were used in all patients of both groups. This consisted of the use of intermittent aortic cross-clamping as the surgical technique for coronary artery bypass grafting, whereas the priming fluid of the CPB circuit contained 2.10^6 kallikrein inhibiting units aprotinin and 1 mg/kg lidoflazine. In addition, all patients had received 2 g methylprednisolone after induction of anesthesia.

During CPB, anesthesia was maintained with remifentanil and TCI propofol in group A and with remifentanil and sevoflurane in group B. 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, the catheters were repositioned in the left atrium and the left ventricle. The heart was paced in atrioventricular sequential mode at a rate of 90 beats/min, and the patients were separated from CPB. When cardiac index was below 2.5 $l \cdot m^{-2} \cdot min^{-1}$, dobutamine was initiated. When mean arterial pressure was below 60 mmHg, vasoconstrictive therapy with phenylephrine was started. After a stabilization period of 15 min to allow for recovery of systolic and diastolic data after CPB, the post-CPB measurements were obtained.[16] After CPB, anesthesia was maintained with remifentanil combined with propofol in group A and sevoflurane in group B. After removal of the aortic canula, heparin activity was neutralized with protamine at a ratio of 1 mg protamine for 100 IU heparin. Protamine administration was further guided by ACT measurements aiming at a value of 140 s. At the end of the surgical procedure, patients were transferred to the intensive care unit where they were kept sedated for 4 h with a continuous infusion of 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil and 2 mg/ml TCI propofol. Then the patients were weaned from the ventilator and extubated.

Hemodynamic Data Analysis

Global hemodynamic data (mean arterial pressure [MAP], mean pulmonary artery pressure [MPAP], central venous pressure [CVP], cardiac output, and systemic vascular resistance [SVR]) were registered just before the start of surgery (BASE), before the start of CPB (pre-CPB), 15 min after the end of CPB (post-CPB), and at the end of the operation (END). Five consecutive beats were averaged.

Left atrial and LV data were recorded before and after CPB. End-diastolic pressure (EDP) was timed at the peak of the R wave on the electrocardiogram. The effects of leg elevation in the different conditions on LV load and function were evaluated by the changes in EDP, peak LV pressure (LVP), LV pressure at dP/dt_{min} (= end-systolic pressure [ESP]), and dP/dt_{max}. Effects of leg elevation on rate of LV pressure fall were evaluated by dP/dt_{min} and the time constant τ of isovolumic relaxation. τ Was

calculated based on the monoexponential model with nonzero asymptote using LV pressure values from dP/dt_{min} to mitral valve opening. The following equation was used: $\ln P_t = \ln P_0 - \text{time}/\tau$. Time constant τ was fit in a linear manner to the corresponding ESP, and the slope R (ms/mmHg) of this relation was calculated. R quantified changes in τ, induced by the changes in ESP and quantified afterload dependence of the rate of LV pressure fall.[14,15,17] At least 10 consecutive beats were taken for the calculation of R. Sample correlation coefficients of the ESP–τ relationships yielded values of $r > 0.92$ in all patients.

Biochemical Analysis

In all patients, blood was sampled for determination of cardiac troponin I. These samples were obtained before the start of surgery (control), at arrival in the intensive care unit (T0), and after 3 (T3), 12 (T12), 24 (T24), and 36 h (T36). Sensitivity of cardiac troponin I determination in the institutional lab is 0.04 ng/ml.

Statistical Analysis

Sample size of the study was calculated based on cardiac troponin concentration as the primary outcome variable. A minimum detected difference of 2 ng/ml between both treatment groups (propofol and sevoflurane) was considered clinically significant. For a power of 0.8 and $\alpha = 0.05$, a sample size of 10 patients in each group was calculated to be appropriate.

Patient characteristics were compared using Fisher exact test and unpaired *t* test analysis where appropriate. Medians were compared using the Mann–Whitney test. Hemodynamic data were tested for normal distribution. Data before and after CPB were compared using a two-way analysis of variance for repeated measurements. Interaction analysis revealed whether effects of CPB were different between groups A and B. Posttest analysis was performed using the Tukey test. Relations in hemodynamic parameters were analyzed using linear regression analysis computing the Pearson correlation coefficient. Because values of troponin I do not have a Gaussian distribution, the data were expressed as median and 95% confidence interval. Troponin I values in both groups were compared using the Mann–Whitney test. All hemodynamic data were expressed as mean ± SD. Statistical significance was accepted at $P < 0.05$. All *P* values were two-tailed.

Results

There were no significant differences in the characteristics of the patients, except for the preoperative ejection fraction, which was slightly higher in the propofol group (table 1). Complete revascularization was performed, and surgery was uneventful in all patients. Both in the operating room and in the intensive care unit, no signs of myocardial infarction or ischemia were observed on the electrocardiogram. Hospital and intensive care unit stays were normal in all patients of both groups, and recovery was uneventful.

Table 1. Patient Characteristics

	Propofol (n = 10)	Sevoflurane (n = 10)
Preoperative data		
Sex (M/F)	8/2	8/2
Age (yr)	63 ± 8	62 ± 10
Length (cm)	176 ± 9	174 ± 7
Weight (kg)	79 ± 13	81 ± 13
BMI (kg/m^2)	25.6 ± 3.1	27.0 ± 3.3
EF (%)	68 ± 5.1	60 ± 9*
Previous AMI	3	4
Hypertension	4	5
Diabetes	1	1
COPD	0	1
Smoking	7	9
Medication		
β Blockers	10	9
Ca channel inhibitors	5	4
ACE inhibitors	5	4
Diuretics	1	2
Antiarrhythmic agents	0	0
Platelet aggregation inhibitors	7	6
Nitrates	8	7
Intraoperative data		
No. of bypasses	3 (3–6)	4 (2–5)
No. of arterial grafts	2 (1–2)	2 (1–2)
Cross-clamp time (min)	44 ± 19	39 ± 9
CPB time (min)	118 ± 54	109 ± 23

Data are mean ± SD; No. of bypasses and arterial grafts are median (range).

* $P < 0.05$ between groups.

BMI = body mass index; EF = ejection fraction; AMI = acute myocardial infarction; COPD = chronic obstructive pulmonary disease; ACE = angiotensin-converting enzyme; CPB = cardiopulmonary bypass.

Mean arterial pressure decreased after CPB in the propofol group but not in the sevoflurane group. MPAP and CVP were kept stable throughout in both groups. Post-CPB cardiac output was decreased in the propofol group but not in the sevoflurane group (table 2).

Figure 1 illustrates the two types of response to leg elevation before and after CPB. Two types of response can be distinguished, improvement of LV function (left panel) *versus* impairment of LV function (right panel).

Left ventricular end-diastolic pressure increased after CPB. The decrease in dP/dt_{max} after CPB was more pronounced in the propofol group (19 ± 4%) than in the sevoflurane group (7 ± 3%) ($P < 0.05$). Peak LV pressure and end-systolic pressure decreased after CPB in the propofol group but not in the sevoflurane group. Maximal rate of pressure decline decreased with CPB in the propofol group but not in the sevoflurane group. After CPB, the time constant of isovolumic relaxation (τ) was significantly lower with sevoflurane than with propofol (table 3).

Table 2. Perioperative Hemodynamic Data

	Base	Pre-CPB	Post-CPB	End
MAP (mmHg)				
Propofol	81 ± 6	74 ± 7	66 ± 5*	70 ± 4*
Sevoflurane	78 ± 4	78 ± 4	76 ± 3†	80 ± 3†
MPAP (mmHg)				
Propofol	21 ± 3	20 ± 3	23 ± 3	23 ± 3
Sevoflurane	21 ± 3	21 ± 3	23 ± 3	22 ± 4
CVP (mmHg)				
Propofol	12 ± 2	11 ± 2	12 ± 2	13 ± 2
Sevoflurane	11 ± 3	11 ± 3	11 ± 3	12 ± 2
Cardiac output (l/min)				
Propofol	5.8 ± 1.1	4.9 ± 0.9	4.5 ± 0.9*	4.7 ± 0.4*
Sevoflurane	5.2 ± 0.7	5.4 ± 0.9	5.6 ± 0.5†	5.6 ± 0.6†
SVR (dyne · s · cm^{-5})				
Propofol	1,008 ± 116	1,017 ± 140	990 ± 175	1,004 ± 107
Sevoflurane	1,021 ± 128	997 ± 179	965 ± 125	992 ± 142

Data are mean ± SD.

* Different compared to base ($P < 0.05$). † Different between propofol and sevoflurane ($P < 0.05$).

CPB = cardiopulmonary bypass; MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; CVP = central venous pressure; SVR = systemic vascular resistance.

Leg elevation increased EDP. The increase in EDP was higher after CPB than before CPB with propofol but not with sevoflurane. Before CPB, the increase in dP/dt_{max} with leg elevation was similar in both groups (1 ± 6% in group A and 5 ± 3% in group B). After CPB, the effects of leg elevation on dP/dt_{max} significantly differed among groups ($P < 0.05$; −5 ± 4% in the propofol group *vs.* +5 ± 4% in the sevoflurane group). Peak LVP increased similarly with leg elevation in both groups before CPB. After CPB, the increase in LVP with leg elevation was less than before CPB, and this effect was most pronounced for the propofol group. The increase in ESP and dP/dt_{min} with leg elevation was similar in the different experimental conditions. The increase in time interval from end

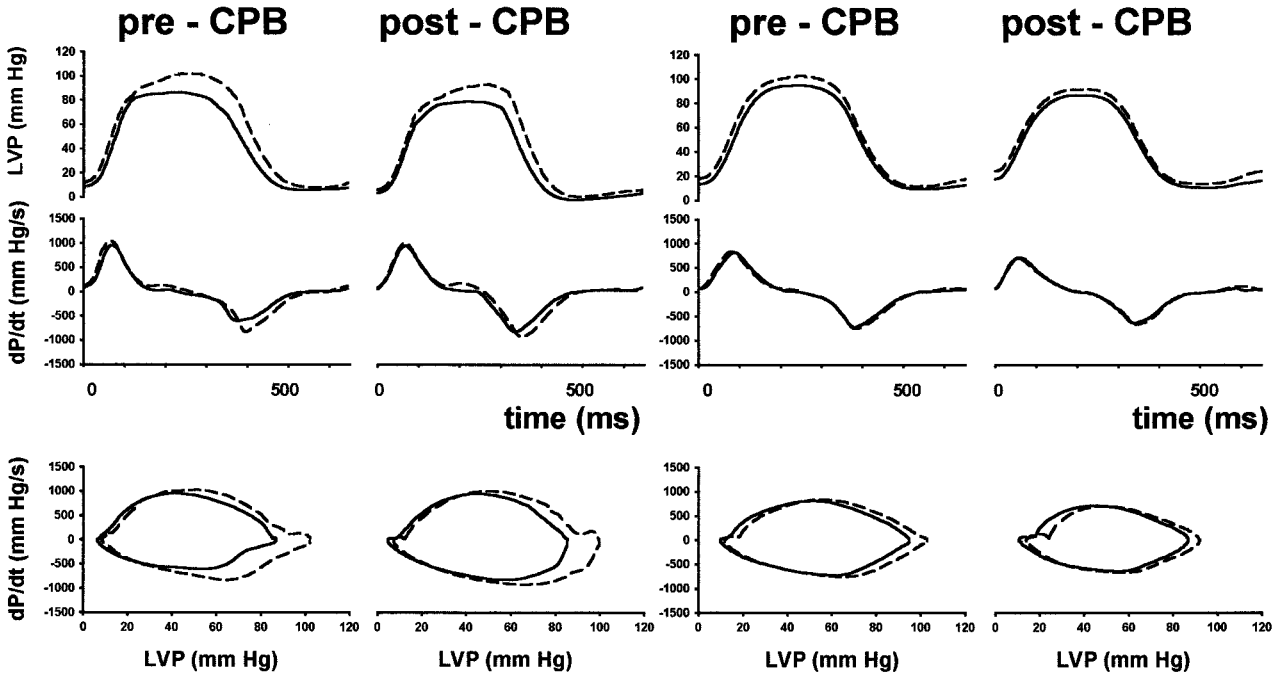

Fig. 1. Representative example of the effects of leg elevation on left ventricular pressure (LVP), dP/dt_{max}, and LVP − dP/dt tracings before and after cardiopulmonary bypass (CPB). Each panel shows two superposed tracings, comparing the baseline condition (solid lines) to the condition at the end of leg elevation (dashed lines). Leg elevation resulted in a variable response of LV function among patients. In the left panel, leg elevation resulted in an improved LV function with an increase in dP/dt_{max} and an acceleration of LV pressure fall. This acceleration is apparent from the LVP − dP/dt tracings at the lower panels of the figure. On such a plot, the cardiac cycle is read clockwise from the left, with pressure rise displayed above the zero line and pressure fall displayed below the zero line. With leg elevation, LV pressure and rate of pressure development and pressure decline increased. In the right panel, leg elevation resulted in impairment of LV function. This is manifested by a decrease in dP/dt_{max} and a deceleration of LV pressure fall.

Table 3. Left Atrial (LA) and Left Ventricular (LV) Pressure (P) Data before and after Cardiopulmonary Bypass (CPB)

	Pre-CPB	Post-CPB
EDP (mmHg)		
Propofol	12 ± 6	14 ± 6*
Sevoflurane	11 ± 3	14 ± 3*
LAP (mmHg)		
Propofol	15 ± 5	14 ± 6
Sevoflurane	13 ± 2	14 ± 4
dP/dt_{max} (mmHg/s)		
Propofol	916 ± 88	676 ± 93*
Sevoflurane	967 ± 95	892 ± 104*†
Peak LVP (mmHg)		
Propofol	95 ± 11	84 ± 7*
Sevoflurane	95 ± 9	92 ± 7†
dP/dt_{min} (mmHg/s)		
Propofol	704 ± 91	580 ± 56*
Sevoflurane	741 ± 102	761 ± 103†
ESP (mmHg)		
Propofol	60 ± 4	50 ± 6*
Sevoflurane	58 ± 6	58 ± 8†
Ejection time (ms)		
Propofol	379 ± 8	325 ± 11*
Sevoflurane	377 ± 9	350 ± 10*†
P at MVO (mmHg)		
Propofol	17 ± 3	18 ± 5
Sevoflurane	17 ± 4	19 ± 4
tau (ms)		
Propofol	61 ± 4	67 ± 3*
Sevoflurane	58 ± 4	61 ± 2†

Data are mean ± SD.

* Different between pre- and post-CPB ($P < 0.05$). † Different between propofol and sevoflurane ($P < 0.05$).

ED = end-diastole; ESP = end-systolic pressure; MVO = mitral valve opening.

diastole to dP/dt_{min} with leg elevation was similar before and after CPB in the sevoflurane group but not in the propofol group. τ Increased after CPB in the propofol group but not in the sevoflurane group. Load dependence of LV pressure fall (R) was similar in both groups before CPB. After CPB, R was increased in the propofol group but not in the sevoflurane group (table 4).

Need for inotropic and vasoconstrictive support was significantly different in both groups. In the propofol group, 4 of the 10 patients needed dobutamine to be successfully weaned from CPB, whereas in the sevoflurane group, only 1 patient needed inotropic support with dobutamine. In the propofol group, 7 patients needed vasoconstrictive therapy with phenylephrine after the end of CPB, whereas in the sevoflurane group, this was the case in only 2 patients.

Figure 2 illustrates the evolution of cardiac troponin I concentrations during the first 36 h postoperatively. Troponin I values were similar in both groups at control, T0, and T3. For the sevoflurane group, troponin I concentrations remained below the cutoff value of 2 ng/ml throughout the observation period. In the propofol group, on the contrary, an elevation in troponin I concentrations was observed at T12, with a peak at T24 followed by a decrease at T36.

Discussion

The results of the present study indicate that the patients anesthetized with sevoflurane had preserved cardiac function after weaning from CPB and lower concentrations of cardiac troponin I than the patients anesthetized with propofol.

Many factors are known to determine occurrence of myocardial damage and outcome after coronary surgery. Among these, patient characteristics and surgery-related events are the most common reasons for possible complications. Patient characteristics were similar in both groups, except for the preoperative ejection fraction, which was slightly less in the sevoflurane group. None of the patients developed angina in the days before surgery. Preoperative and perioperative anticoagulation therapy was similar and surgery was uneventful in all patients with a complete revascularization and no signs of ischemia or myocardial infarction on the electrocardiogram at any time. Number of grafts, type of cardioprotection, duration of aortic cross-clamp time, and CPB were also similar in all patients. This suggests that the differences

Table 4. Changes in Left Atrial (LA) and Left Ventricular (LV) Pressure (P) Data with Leg Elevation before and after Cardiopulmonary Bypass (CPB)

	Pre-CPB	Post-CPB
Δ EDP (mmHg)		
Propofol	5 ± 3	8 ± 2*
Sevoflurane	3 ± 1	4 ± 1†
Δ LAP (mmHg)		
Propofol	3 ± 1	4 ± 2
Sevoflurane	3 ± 1	2 ± 1
Δ dP/dt_{max} (mmHg/s)		
Propofol	13 ± 50	−30 ± 49*
Sevoflurane	47 ± 36	34 ± 29†
Δ Peak LVP (mmHg)		
Propofol	11 ± 3	5 ± 4*
Sevoflurane	12 ± 3	9 ± 2*†
Δ dP/dt_{min} (mmHg/s)		
Propofol	80 ± 47	52 ± 51
Sevoflurane	93 ± 53	66 ± 30
Δ ESP (mmHg)		
Propofol	6 ± 3	5 ± 3
Sevoflurane	8 ± 3	6 ± 2
Δ Ejection time (ms)		
Propofol	13 ± 5	7 ± 6*
Sevoflurane	11 ± 7	8 ± 8
Δ P at MVO (mmHg)		
Propofol	4 ± 2	4 ± 3
Sevoflurane	4 ± 1	4 ± 1
Δ tau (ms)		
Propofol	1 ± 2	4 ± 2*
Sevoflurane	0 ± 2	1 ± 2†
R (ms/mmHg)		
Propofol	0.48 ± 0.53	0.84 ± 0.59*
Sevoflurane	0.28 ± 0.29	0.29 ± 0.39†

Data are mean ± SD.

* Different between pre- and post-CPB ($P < 0.05$). † Different between propofol and sevoflurane ($P < 0.05$).

ED = end-diastole; MVO = mitral valve opening; R = afterload dependency of LV pressure fall.

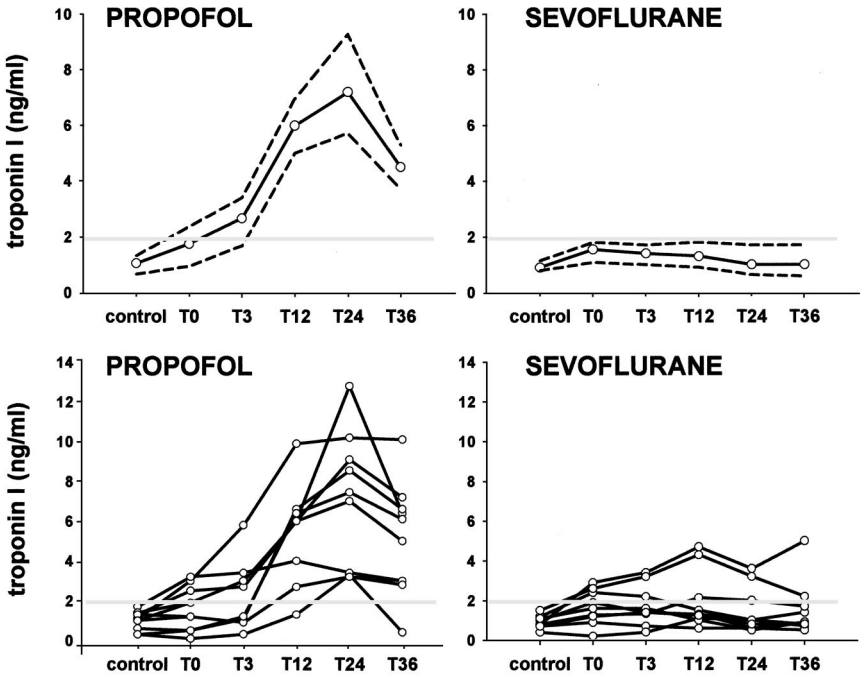

Fig. 2. Cardiac troponin I concentrations in the propofol and sevoflurane groups before surgery (control), at arrival in the intensive care unit (T0), and after 3 (T3), 12 (T12), 24 (T24), and 36 h (T36). The upper panels show the median values with 95% confidence intervals. The lower panels show the evolution of the individual values. Concentrations were significantly higher with propofol. In the propofol group, all patients had troponin concentrations above the cutoff value off 2 ng/ml (gray line).

in cardiac function between both groups are not caused by differences in patient characteristics and intraoperative events but instead seem be related to the choice of the anesthetic agent.

The underlying mechanism for the different responses with the two agents cannot be elucidated from the present study. Both propofol and sevoflurane were administered throughout the whole operation. Therefore, it is not possible to distinguish between preconditioning effects and protection against reperfusion injury and/or stunning. Recent evidence suggested that volatile anesthetics exert protective effects during myocardial ischemia and reperfusion. The mechanisms for these cardioprotective effects are similar to those observed during ischemic preconditioning.[2–4,5,18] In addition to its preconditioning effects, sevoflurane also appears to exhibit cardioprotective effects against reperfusion injury. This effect has been attributed to its radical scavenging properties and the reduction of postischemic adhesion of neutrophils.[19,20] Experimental observations have also indicated a cardioprotective effect of sevoflurane against myocardial stunning.[21] The assumption that the reduction of stunning might contribute to the improved cardiac function is supported by the fact that patients anesthetized with sevoflurane needed less inotropic support. Finally, sevoflurane was shown to reduce the ischemia-induced metabolic changes in the myocardium, associated with decreased systemic hemodynamic parameters. It was suggested that this protective effect on ischemic myocardium may be partly due to the hemodynamic effects of sevoflurane but also to a possible direct effect on ischemic myocardium.[22] The reports on the possible cardioprotective effects of propofol are less straightforward. Although a number of studies have suggested that propofol may exhibit free radical scavenging properties,[23,24] other studies have failed to demonstrate a protective effect of propofol on myocardial function during ischemia and reperfusion.[25,26]

It should be noted that in the present observations, both propofol and sevoflurane were used as part of a multidrug anesthetic regimen. Opioids were also shown to mimic the cardioprotective effect of ischemic preconditioning.[27] 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 both groups, suggesting that the observed differences in cardiac function between both might be related to the choice between propofol and sevoflurane.

Antidiabetic agents of the sulfonylurea type can block the cardioprotection induced by both ischemic and pharmacologic preconditioning. The same is true for theophylline, which blocks adenosine release, thereby possibly influencing preconditioning mechanisms. However, none of the patients included received this type of medication. A number of patients, especially in the propofol group, needed inotropic and vasoconstrictive support. It is obvious that these drugs have interfered with the analysis of cardiac function after CPB, resulting in improved myocardial contractility. The current data may therefore not be interpreted as net effects of propofol or sevoflurane anesthesia on cardiac function after CPB.

Analysis of cardiac function did not only include baseline measurements but also an evaluation of the cardiac functional reserve capacity of the ventricle. All patients in the current study had a baseline cardiac function that

could be qualified as near normal. Nevertheless, a number of patients developed impairment of LV function when subjected to an increase in cardiac load. These patients developed a decrease in maximal rate of pressure development (dP/dt_{max}) and a delayed myocardial relaxation with enhanced load dependence of LV pressure fall. This latter response is indicative for a deficient length-dependent regulation of myocardial function,[15] indicating that despite their normal values of baseline ejection fraction, these patients had impaired LV function. In the patients anesthetized with sevoflurane, neither baseline parameter of LV function as the response to increased cardiac load was altered after CPB. In the patients anesthetized with propofol, on the other hand, not only were baseline parameters of LV function decreased after CPB, but the response to an increase in cardiac load was also impaired.

Cardiac troponin I is known as a sensitive marker for myocardial cellular damage.[28,29] Postoperative values of these enzymes were lower in the sevoflurane than in the propofol group, which is consistent with a cardioprotective effect of sevoflurane in the current clinical setting. Although troponin I concentrations were increased with propofol and clearly above the cutoff value of 2 ng/ml, they still compare favorably with the value of 5.2 μg/l reported by Sadony *et al.*[30] in patients classified as having minor myocardial damage and certainly with the cutoff value of 13.4 μg/l reported by Jacquet *et al.*[31] to significantly separate patients with an uneventful recovery from those with myocardial ischemia and infarction.

Several methodologic issues deserve attention. The current data were obtained in patients with preserved baseline cardiac function (preoperative ejection fraction ~60%). Further studies will have to evaluate whether the present observations also hold for patients with lower preoperative ejection fractions. Heart rate during the protocol was regulated with cardiac pacing. The use of pacing discarded variations in heart rate between patients and within the same patient as a confounding factor. The current data were obtained in the presence of an open chest, open pericardium. After pericardiotomy, a rightward shift of the EDP–dimension relationship occurs with improvement of the Frank-Starling mechanism compared to closed-chest conditions.[32,33] It was recently shown that the cardioprotective effects of sevoflurane may depend upon the concentration used. One minimum alveolar concentration (MAC) sevoflurane reduced infarct size after regional ischemia in the rat heart *in vivo*. A lower concentration of 0.75 MAC had no effect on infarct size, whereas a higher concentration of 2 MAC did not result in further protection.[34] The concentrations of sevoflurane in the current study ranged between 0.5 and 1 MAC. The present study sample size did not permit to relate possible differences in cardioprotective effects to the concentration range used. Further studies will therefore have to evaluate whether cardioprotective effects of sevoflurane in the clinical setting are dose-dependent. It is also important to note that despite the differences in early postoperative cardiac function and troponin I concentrations, clinical outcome and hospital stay did not differ between groups. Further larger multicenter studies will therefore have to elucidate whether the long-term clinical outcome may be influenced by the choice of the anesthetic agent in different subsets of patients.

In conclusion, in coronary surgery patients, anesthesia with sevoflurane preserved cardiac function after CPB, suggesting that sevoflurane may have protective properties during coronary surgery. The cardioprotective effects of sevoflurane during ischemia and reperfusion reported in experimental conditions therefore appear to have clinical implications.

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