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Cardioprotective Properties of Sevoflurane in Patients Undergoing Coronary Surgery with Cardiopulmonary Bypass Are Related to the Modalities of Its Administration

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Background: **Experimental studies have related the cardioprotective effects of sevoflurane both to preconditioning properties and to beneficial effects during reperfusion. In clinical studies, the cardioprotective effects of volatile agents seem more important when administered throughout the procedure than when used only in the preconditioning period. The authors hypothesized that the cardioprotective effects of sevoflurane observed in patients undergoing coronary surgery with cardiopulmonary bypass are related to timing and duration of its administration.**

Methods: **Elective coronary surgery patients were randomly assigned to four different anesthetic protocols (n = 50 each). In a first group, patients received a propofol based intravenous regimen (propofol group). In a second group, propofol was replaced by sevoflurane from sternotomy until the start of cardiopulmonary bypass (SEVO pre group). In a third group, propofol was replaced by sevoflurane after completion of the coronary anastomoses (SEVO post group). In a fourth group, propofol was administered until sternotomy and then replaced by sevoflurane for the remaining of the operation (SEVO all group). Postoperative concentrations of cardiac troponin I were followed during 48 h. Cardiac function was assessed perioperatively and during 24 h postoperatively.**

Results: **Postoperative troponin I concentrations in the SEVO all group were lower than in the propofol group. Stroke volume decreased transiently after cardiopulmonary bypass in the propofol group but remained unchanged throughout in the SEVO all group. In the SEVO pre and SEVO post groups, stroke volume also decreased after cardiopulmonary bypass but returned earlier to baseline values than in the propofol group. Duration of stay in the intensive care unit was lower in the SEVO all group than in the propofol group.**

Conclusion: **In patients undergoing coronary artery surgery with cardiopulmonary bypass, the cardioprotective effects of sevoflurane were clinically most apparent when it was administered throughout the operation.**

EXPERIMENTAL data have indicated that anesthetic agents may exert cardioprotection, independently from their effects on coronary blood flow or cardiac work. On one hand, volatile anesthetics have been shown to have a preconditioning-like effect, resulting in protection against myocardial infarction and irreversible myocardial dysfunction.[1–6] On the other hand, volatile anesthetics have also been shown to provide protection against reperfusion injury when administered after myocardial ischemia.[7–9] Few studies have compared the relative importance of the myocardial protective effects of volatile anesthetics when administered before ischemia or during reperfusion and have reported conflicting results. In a study on isolated guinea pig hearts, Varadarajan *et al.*[10] observed that sevoflurane initiated a maximal protective effect before ischemia that overrode the lesser protective effect of the agent on reperfusion. However, in another study on anesthetized rats, Obal *et al.*[11] observed a stronger cardioprotective effect when sevoflurane was administered during reperfusion than after its administration as a preconditioning stimulus.

Several clinical studies in coronary surgery patients have addressed the potential clinical implications of these cardioprotective effects on postoperative myocardial function. The majority of these studies involved a preconditioning protocol in which a volatile anesthetic was administered before myocardial ischemia occurred.[12–16] Although most of these studies reported some cardioprotective effects, the magnitude and extent of this protection was variable. Another group of studies evaluated the effects of volatile anesthetics administered throughout the procedure.[17–20] In these latter studies, an improved myocardial function and a lower release of biochemical markers of damage in the postoperative period was observed, demonstrating a significant cardioprotective effect associated with the use of a volatile anesthetic regimen.

Discrepancies observed in the importance of the cardioprotection afforded by these different protocols could be related to the fact that the duration and timing of administration of volatile anesthetics is one of the factors contributing to the extent of myocardial protection. We therefore hypothesized that the postoperative release of biochemical markers of myocardial damage would be lower and that immediate postoperative myocardial function would be better when the agent was administered throughout the procedure than when administered only during a limited period before ischemia or after completion of the coronary anastomoses. To test this hypothesis, we compared postoperative concentrations of troponin I and indexes of myocardial function in

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patients undergoing coronary surgery with cardiopulmonary bypass (CPB) under four different anesthetic protocols: intravenous regimen with propofol throughout, sevoflurane only before CPB, sevoflurane only after completion of the coronary anastomoses, and sevoflurane throughout.

Materials and Methods

Patient Population

The study was approved by the institutional ethical committee (University Hospital Antwerp, Edegem, Belgium), and written informed consent was obtained. Two hundred patients scheduled to undergo elective coronary surgery with CPB were enrolled. Preoperative exclusion criteria included previous coronary or valvular heart surgery, combined operations (simultaneous valve repair, carotid endarterectomy, or left ventricular [LV] aneurysm repair), unstable angina, valve insufficiency, documented myocardial infarction within the previous 6 weeks, active congestive heart failure, hemodynamic instability with the need for medical or mechanical support, severe hepatic disease (alanine aminotransferase or aspartate aminotransferase $>$ 150 U/l), renal insufficiency (creatinine concentration $>$ 1.5 mg/dl), severe chronic obstructive pulmonary disease (forced expired volume in 1 s $<$ 0.8 l), or history of neurologic disturbances.

Antiplatelet therapy (acetylsalicylic acid and thienopyridines) was stopped 1 week before operation and replaced by a daily dose of nadroparine (Fraxiparine®; Sanofi-Synthelabo, Brussels, Belgium), 0.6 ml (5,700 U anti-Xa) subcutaneously. Sulfonylurea derivatives were stopped 2 days before the operation and replaced by insulin therapy if necessary. None of the patients included were receiving theophylline therapy.

Study Groups

Patients were randomly allocated to four different anesthetic protocols. A computer-generated random code determined 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 and the ward were blinded to the group assignments.

Anesthetic Protocols

All preoperative cardiac medication was continued until the morning of surgery, except for the angiotensin-converting enzyme inhibitors. All patients received standard premedication of 2.5 mg sublingual lorazepam (Temesta Expidet®; AHP Pharma, Louvain-la-Neuve, Belgium) 90 min before surgery and 1 μg/kg intramuscular fentanyl and 50 μg/kg droperidol 60 min before surgery.

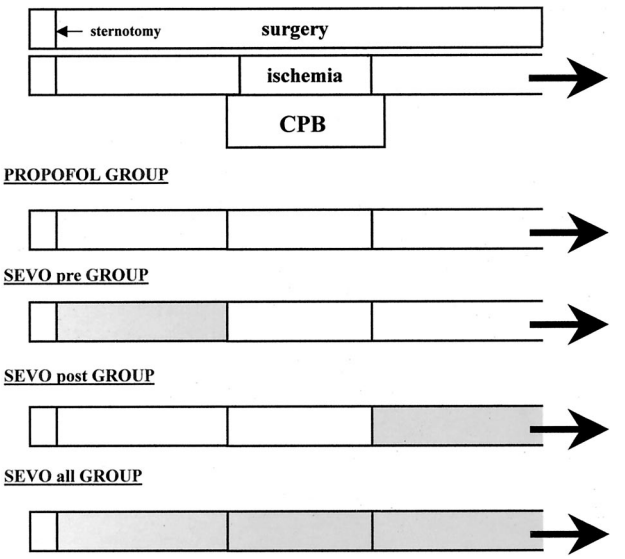

Fig. 1. Schematic representation of the different anesthetic protocols used in the current study. In all groups, propofol was administered until sternotomy. The filled boxes represent the time that sevoflurane was administered in the different protocols. CPB = cardiopulmonary bypass.

In all groups (n = 50 each), anesthesia was induced with a continuous infusion of remifentanil (Ultiva®; GlaxoSmithKline, Genval, Belgium) at 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and a target-controlled infusion of propofol (Diprivan®; AstraZeneca, Brussels, Belgium) set at a target plasma concentration of 2 μg/ml. Anesthesia was maintained with 0.2–0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil and a target-controlled infusion of propofol set at a plasma target concentration of 2–4 μg/ml. Muscle relaxation was obtained with 0.1 mg/kg pancuronium bromide (Pavulon®; Organon, Brussels, Belgium).

In the first group, this regimen was maintained throughout the operative period (propofol group). In the second group, propofol was stopped and replaced by 0.5–2% sevoflurane (Sevorane®; Abbott, Louvain-la-Neuve, Belgium) after sternotomy until the start of CPB. At that moment, sevoflurane was stopped, and propofol was reinitiated for the remainder of the procedure (SEVO pre group). In the third group, propofol was discontinued from the opening of the internal thoracic artery anastomosis and replaced by 0.5–2% sevoflurane until the end of the operation (SEVO post group). In the fourth group, propofol was discontinued after the sternotomy and replaced by 0.5–2% sevoflurane for the remainder of the operation (SEVO all group) (fig. 1).

Perioperative Procedures

In the operating room, patients received routine monitoring including five-lead electrocardiogram, radial and pulmonary artery catheters with continuous cardiac output measurement (Swan Ganz CCO/VIP; Edwards Life-

sciences LLC, Irvine, CA), pulse oximetry, capnography, and blood and urine bladder temperature monitoring. In all patients, Bispectral Index monitoring (BIS® A2000 system; Aspect Medical Systems, Newton, MA) was applied. The concentration of anesthetic agents in all groups was titrated to maintain a Bispectral Index value less than 50 throughout the procedure.

Routine surgical technique and cardioprotective strategies were used in all patients of all groups. This included intravenous administration of 2 g methylprednisolone after induction of anesthesia and the high-dose aprotinin (Trasylol®; Bayer, Leverkusen, Germany) scheme (bolus of 2×10^6 kallikrein inhibiting units followed by a continuous infusion of 5×10^5 kallikrein inhibiting units/h until the end of CPB plus an additional 2×10^6 kallikrein inhibiting units in the priming fluid of the CPB circuit). The CPB circuit used was a closed system consisting of tubing with a surface-modifying additives coating, an arterial filter with heparin coating, a hollow fiber membrane oxygenator with a surface-modified additives coating, and a venous and cardiotomy reservoir (Cobe Cardiovascular Inc., Arvada, CO). The priming fluid of the CPB circuit contained 1,000 ml hydroxyethyl starch, 6%, 130/0.4 (Voluven®; Fresenius Kabi, Schelle, Belgium); 300 ml crystalloids (Plasma-Lyte®; Baxter, Lessines, Belgium); 200 ml aprotinin; 5,000 U heparin; and 1 mg/kg lidoflazine (a nucleoside transport inhibitor; Johnson & Johnson, Beerse, Belgium). Patients had median sternotomy with harvesting of saphenous veins and internal thoracic arteries as conduits. All patients received 300 U/kg heparin (Heparine®; Leo Pharma, Zaventem, Belgium) before the start of CPB. Activated coagulation time (using kaolin as activator) was kept above 450 s throughout the CPB period. After the start of CPB, a venting catheter was inserted into the LV cavity through the right superior pulmonary vein. Then the heart was totally decompressed, and the first venous graft was prepared before the aorta was cross clamped for the first time. Systemic temperature was allowed to drift during CPB to 32°C. Hematocrit concentrations were maintained between 20 and 25%, and CPB flow was maintained between 2.2 and 2.5 $l \cdot min^{-1} \cdot m^{-2}$. The mean perfusion pressure was kept at 50–60 mmHg. Revascularization was performed using intermittent aortic cross clamping as surgical technique for coronary artery bypass grafting.

After the surgical procedure, reperfusion of the heart (total reperfusion time on CPB was set at 50% of the aortic cross clamp time in all patients), and rewarming to a bladder temperature of 35°C, 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 $2.0 l \cdot m^{-2} \cdot min^{-1}$, dobutamine was initiated. When mean arterial pressure was below 60 mmHg, vasoconstrictive therapy with phenylephrine was started. After 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 s. At the end of the surgical procedure, patients were transferred to the intensive care unit, where they were kept sedated with a continuous infusion of $0.3 \mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil and 2 μg/ml propofol. When hemodynamically stable and rewarmed, the patients were weaned from the ventilator and extubated.

Hemodynamic Data Analysis

Global hemodynamic data (mean arterial pressure, mean pulmonary artery pressure, central venous pressure, cardiac output, stroke volume, and systemic vascular resistance) were registered just before the start of surgery (baseline), before the start of CPB (pre-CPB), 15 min after the end of CPB (post-CPB),[21] at the end of the operation, 6 h after installation in the intensive care unit (T6), and 12 (T12) and 24 h (T24) later. Cardiac output data for the study protocol were measured using the bolus thermodilution method by injecting 10 ml cold saline at end-expiration. Three measurements within 10% of each other were averaged, and this value represented the cardiac output at that time of measurement.

In each group, the 20 first patients were in addition instrumented with sterilized, prezeroed electronic tipmanometers (MTCP3Fc catheter; Dräger Medical Electronics, Best, The Netherlands; frequency response = 100 KHz). The catheter was positioned through the right superior pulmonary vein and the left atrium in the LV cavity and 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 setting 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 patient's legs. Leg elevation resulted in a rapid beat-to-beat increase in LV pressures.

A first set of measurements was obtained before CPB. After this measurement, the catheters were removed, the venous cannula was inserted, and CPB was initiated. After the surgical procedure, reperfusion of the heart, and rewarming, the catheter was repositioned in the left ventricle. LV data were recorded before and after CPB. End-diastolic pressure was timed at the peak of the R

wave on electrocardiography. The effects of leg elevation in the different conditions on LV load and function were evaluated by the changes in end-diastolic pressure, peak LV pressure, LV pressure at dP/dt_{min} (= end-systolic pressure), and dP/dt_{max}. Effects of leg elevation on rate of LV pressure decrease 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 a cutoff value of 10 mmHg higher than end-diastolic pressure.[22,23] The following equation was used: $\ln P_t = \ln P_0 - \text{time}/\tau$. Time constant τ was linearly fit to the corresponding end-systolic pressure, and the slope R (ms/mmHg) of this relation was calculated. R quantified changes in τ, induced by the changes in end-systolic pressure and quantified afterload dependence of the rate of LV pressure decrease.[24–26] At least 10 consecutive beats were taken for the calculation of R. Sample correlation coefficients of the end-systolic pressure–τ relations yielded values of $r > 0.92$ in all patients.

Biochemical Analysis

In all patients, blood was sampled for determination of cardiac troponin I and serum creatinine. These samples were obtained before surgery (baseline) at arrival in the intensive care unit (T0) and after 6 (T6), 12 (T12), 24 (T24), and 48 h (T48). Troponin I was measured using an immunoassay method (Vitros ECI®; Orthoclinical Diagnostics, Beerse, Belgium). The limit of quantification of cardiac troponin I determination was 0.04 ng/ml. When values below the detection limit were reported, zero was retained as the value. The coefficient of variation of the measurements is 15% for troponin I values up to 0.06 ng/ml, 7% for values between 0.77 and 3.37 ng/ml, and 5% for values above 3.37 ng/ml.

Data Collection and Analysis

All data were collected by trained observers who did not participate in patient care and who were blinded to the anesthetic regimen used. Medical treatment and decision making in the intensive care unit were performed by physicians who were blinded to the type of anesthetic protocol used.

Statistical Analysis

Sample size of the study was calculated on cardiac troponin I concentration at 24 h postoperatively as the primary outcome variable. A minimum detected difference of 2 ng/ml between the different treatment groups was considered clinically significant. For a power of 0.8 and an α of 0.05, a sample size of 50 patients in each group was calculated to be appropriate. Secondary outcome variables were stroke volume and dP/dt_{max} after CPB. For the stroke volume after CPB, a minimum detected difference of 10 ml between the different treatment groups was considered statistically significant. For a power of 0.8 and an α of 0.05, a sample size of 25 patients in each group was calculated to be appropriate. For the dP/dt_{max} after CPB, a minimum detected difference of 100 mmHg/s between the different treatment groups was considered statistically significant. For a power of 0.8 and an α of 0.05, a sample size of 19 patients in each group was calculated to be appropriate.

Sample size calculation and statistical analysis were performed using the SigmaStat 2.03 software package (SPSS, Leuven, Belgium). Patient characteristics were compared using one-way analysis of variance and chi-square analysis where appropriate. Medians were compared using the Kruskal-Wallis one-way analysis of variance test on ranks. Hemodynamic data were tested for normal distribution and were compared using an analysis of variance for repeated measurements. Interaction analysis revealed whether effects were different among groups. Posttest analysis was performed using the Bonferroni–Dunn test. All hemodynamic data were expressed as mean ± SD. Statistical significance was accepted at $P < 0.05$. All P values were two-tailed.

Results

Adequacy of randomization was examined by comparison of group characteristics that might influence outcome variables. Table 1 summarizes preoperative and intraoperative patient characteristics. There were no differences in any of the data recorded. Extent of coronary artery disease and consequently number of grafts, and duration of the various phases of the operation were comparable in the different groups. By randomization, each primary anesthetic regimen was equally distributed among each surgeon's patients.

Troponin I concentrations are displayed in figure 2. Troponin I increased transiently with all anesthetic regimens used, but compared with the propofol group, this increase was significantly lower only in the SEVO all group. Chi-square analysis indicated that the proportion of patients who had a postoperative troponin I increase greater than 2 ng/ml was significantly ($P < 0.001$) related to the anesthetic regimen used (propofol group, n = 36; SEVO pre group, n = 25; SEVO post group, n = 23; SEVO all group, n = 15). For all SEVO groups, the number of patients with a troponin I concentration greater than 2 ng/ml was different from the propofol group (propofol *vs.* SEVO pre, $P = 0.04$; propofol *vs.* SEVO post, $P = 0.02$; propofol *vs.* SEVO all, $P < 0.001$). In the current study population, no significant difference was observed in the number of patients with a troponin I concentration greater than 2 ng/ml among the different SEVO groups. However, the power of the performed statistical test for these comparisons was below the desired power of 0.8; therefore, the sample size was not sufficient to address this issue, and these latter negative findings should be interpreted cautiously.

Table 1. Patient Characteristics

	Propofol (n = 50)	Sevoflurane Pre (n = 50)	Sevoflurane Post (n = 50)	Sevoflurane All (n = 50)
Preoperative data				
Sex, M/F	40/10	40/10	41/9	39/11
Age, yr	66 ± 10	67 ± 11	65 ± 10	65 ± 9
Body mass index, kg/m^2	27.6 ± 4.2	27.7 ± 4.5	27.7 ± 4.7	27.0 ± 3.8
Ejection fraction, %	66 ± 11	64 ± 11	62 ± 9	61 ± 13
Diabetes	12	11	12	10
COPD	4	4	5	6
EuroSCORE, median (range)	3.5 (0–12)	3.5 (0–9)	3 (0–9)	3.5 (0–11)
Long-term preoperative medication				
β Blockers	38	36	40	37
Calcium channel blockers	12	12	11	13
ACE inhibitors	16	18	18	16
Nitrates	21	22	22	22
Molsidomine	13	11	12	11
Diuretics	11	10	10	10
Sulfonylurea	6	6	5	6
Insulin	7	6	7	6
Bronchodilating agents	4	4	5	6
Acetyl salicylic acid	30	32	33	31
LMWH	14	15	16	13
Thienopyridines	7	6	7	7
Dipyridamole	2	2	2	2
Intraoperative data				
No. of bypasses, median (range)	4 (2–6)	4 (2–6)	4 (2–6)	4 (2–6)
No. of arterial grafts, median (range)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)
Aortic cross clamp time, min	28 ± 13	35 ± 12	34 ± 19	31 ± 15
CPB time, min	95 ± 28	104 ± 39	108 ± 40	97 ± 26
Pre-CPB time, min	24 ± 7	24 ± 9	25 ± 8	26 ± 7
Post-CPB time, min	58 ± 11	61 ± 9	58 ± 12	56 ± 10

Data are presented as mean ± SD, unless noted otherwise.

There were no differences among the four groups in any of the preoperative and intraoperative patient characteristics.

ACE = angiotensin-converting enzyme; COPD = chronic obstructive pulmonary disease; CPB = cardiopulmonary bypass; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LMWH = low-molecular-weight heparin. post-CPB time = time from end CPB to end of surgery; pre-CPB time = time from sternotomy to start of CPB.

Systemic hemodynamic data with the four different anesthetic regimens are displayed in table 2. Mean arterial pressure, mean pulmonary arterial pressure, and central venous pressure were kept constant throughout the observation period. Before CPB, heart rate was comparable in the different groups. From after CPB onward, all data were obtained with a fixed heart rate of 90 beats/min. In the propofol group, cardiac output remained

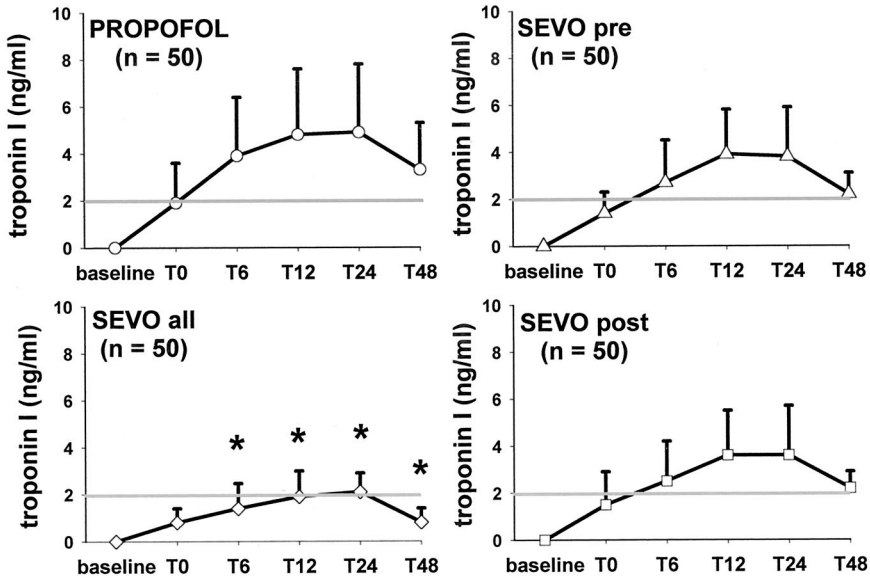

Fig. 2. Cardiac troponin I concentrations in the four groups before surgery (baseline), at arrival in the intensive care unit (T0), and after 6 (T6), 12 (T12), 24 (T24), and 48 h (T48). Data are presented as mean ± SD. * statistically significant difference with the propofol group ($P < 0.05$). In all groups, a transient increase in troponin I concentrations was observed. Only in the SEVO all group, this increase was significantly less than in the propofol group. For the sake of clarity, the SD bars are represented in only one direction.

Table 2. Perioperative and Postoperative Hemodynamic Data

	Baseline	Pre-CPB	Post-CPB	End	ICU T6	ICU T12
MAP, mmHg						
Propofol	71 ± 11	72 ± 9	72 ± 11	74 ± 9	75 ± 11	78 ± 9
SEVO pre	71 ± 10	70 ± 8	70 ± 8	74 ± 8	76 ± 9	79 ± 10
SEVO post	70 ± 10	71 ± 9	71 ± 9	72 ± 9	75 ± 8	79 ± 9
SEVO all	70 ± 9	70 ± 10	74 ± 10	76 ± 9	78 ± 9	80 ± 10
PCWP, mmHg						
Propofol	15 ± 3	16 ± 4	17 ± 3	17 ± 3	17 ± 3	16 ± 4
SEVO pre	14 ± 3	15 ± 3	15 ± 3	16 ± 2	16 ± 2	15 ± 3
SEVO post	15 ± 3	16 ± 3	16 ± 4	15 ± 4	16 ± 3	15 ± 3
SEVO all	15 ± 4	15 ± 3	14 ± 3	15 ± 3	14 ± 3	14 ± 3
CVP, mmHg						
Propofol	10 ± 3	11 ± 2	11 ± 2	11 ± 3	11 ± 2	10 ± 3
SEVO pre	11 ± 2	10 ± 2	11 ± 3	10 ± 3	10 ± 2	10 ± 2
SEVO post	11 ± 3	11 ± 2	10 ± 3	11 ± 3	10 ± 3	10 ± 3
SEVO all	11 ± 2	11 ± 3	10 ± 3	10 ± 3	10 ± 3	9 ± 3
HR, beats/min						
Propofol	66 ± 12	69 ± 14	90 ± 0*	90 ± 0*	90 ± 0*	90 ± 0*
SEVO pre	65 ± 13	68 ± 11	90 ± 0*	90 ± 0*	90 ± 0*	90 ± 0*
SEVO post	65 ± 13	68 ± 11	90 ± 0*	90 ± 0*	90 ± 0*	90 ± 0*
SEVO all	68 ± 14	70 ± 10	90 ± 0*	90 ± 0*	90 ± 0*	90 ± 0*
CO, l/min						
Propofol	4.5 ± 1.1	4.3 ± 1.2	4.7 ± 1.2	4.7 ± 1.1	4.9 ± 1.0	5.5 ± 1.3*
SEVO pre	4.4 ± 1.0	4.3 ± 1.1	5.0 ± 0.9	5.1 ± 0.9	5.7 ± 0.5*†	5.9 ± 1.1*
SEVO post	4.3 ± 1.0	4.4 ± 1.1	4.9 ± 0.8	5.0 ± 0.9	5.7 ± 0.9*†	5.9 ± 0.9*
SEVO all	4.5 ± 0.9	4.6 ± 1.1	5.9 ± 0.9*†	5.9 ± 0.9*†	6.1 ± 0.8*†	6.1 ± 1.1*
SV, ml/beat						
Propofol	65 ± 6	61 ± 6	52 ± 7*	53 ± 6*	55 ± 6*	62 ± 7
SEVO pre	65 ± 9	63 ± 9	55 ± 6*	57 ± 5*	62 ± 4†	65 ± 5
SEVO post	63 ± 5	61 ± 5	53 ± 4*	55 ± 6*	62 ± 6†	64 ± 5
SEVO all	62 ± 5	63 ± 7	64 ± 4†	65 ± 5†	66 ± 5†	67 ± 5
SVR, dyn · s · cm^{-5}						
Propofol	1,023 ± 185	1,034 ± 178	1,006 ± 139	1,011 ± 189	1,002 ± 141	998 ± 182
SEVO pre	1,036 ± 162	1,025 ± 217	1,001 ± 207	1,007 ± 143	987 ± 196	995 ± 216
SEVO post	1,027 ± 222	1,021 ± 207	1,015 ± 188	991 ± 211	977 ± 248	963 ± 206
SEVO all	1,028 ± 185	1,016 ± 213	957 ± 214	927 ± 191	931 ± 239	926 ± 176
Temperature, °C						
Propofol	36.2 ± 0.3	36.2 ± 0.4	36.2 ± 0.4	36.3 ± 0.3	36.4 ± 0.3	36.5 ± 0.4
SEVO pre	36.3 ± 0.3	36.3 ± 0.3	36.3 ± 0.4	36.4 ± 0.4	36.3 ± 0.4	36.5 ± 0.3
SEVO post	36.3 ± 0.4	36.2 ± 0.4	36.2 ± 0.3	36.2 ± 0.3	36.5 ± 0.4	36.5 ± 0.4
SEVO all	36.2 ± 0.5	36.3 ± 0.3	36.2 ± 0.2	36.4 ± 0.3	36.4 ± 0.3	36.5 ± 0.3

Data are presented as mean ± SD.

* Different compared with baseline ($P < 0.05$). † Different from the propofol group ($P < 0.05$).

CO = cardiac output; CPB = cardiopulmonary bypass; CVP = central venous pressure; HR = heart rate; ICU = intensive care unit; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; SEVO = sevoflurane; SV = stroke volume; SVR = systemic vascular resistance.

unchanged until time T6, whereas in the SEVO all group, cardiac output increased after CPB. This implies that stroke volume decreased transiently after CPB in the propofol group with a return to baseline values by T12 and remained unchanged in the SEVO all group. In the SEVO pre and SEVO post groups, stroke volume also decreased after CPB but returned to baseline values from time point T6.

Left ventricular pressure data are summarized in table 3. LV end-diastolic pressure increased after CPB. After CPB, dP/dt_{max}, dP/dt_{min}, peak LV pressure, and end-systolic pressure decreased in all groups except the SEVO all group. Time constant of isovolumic relaxation τ increased in all groups but remained unchanged in the SEVO all group.

The effects of leg elevation on LV pressure data are summarized in table 4. The increase in end-diastolic was higher after CPB than before CPB in all groups except the SEVO all group. Before CPB, leg elevation slightly increased dP/dt_{max} in all four groups. After CPB, leg elevation decreased dP/dt_{max} in all groups except the SEVO all group. Compared with before CPB, this different response was statistically significant in the propofol group but not in the SEVO pre group and the SEVO post group (fig. 3). Before CPB, peak LV pressure increased similarly with leg elevation in all groups. After CPB, the increase in peak LV pressure was lower than before CPB in the propofol, SEVO pre, and SEVO post groups but not in the SEVO all group. The increase in end-systolic pressure and dP/dt_{min} with leg elevation was similar in all groups both before and after CPB. τ increased with leg elevation after CPB in the propofol, SEVO pre, and

Table 3. LVP Data before and after CPB (n = 20/Group)

	Pre-CPB	Post-CPB
EDP, mmHg		
Propofol	10 ± 3	15 ± 2*
SEVO pre	10 ± 3	15 ± 3*
SEVO post	11 ± 3	14 ± 3*
SEVO all	10 ± 3	13 ± 2*
dP/dt_{max}, mmHg/s		
Propofol	973 ± 81	751 ± 88*
SEVO pre	953 ± 73	825 ± 87*
SEVO post	947 ± 75	843 ± 93*
SEVO all	961 ± 72	927 ± 81†
Peak LVP, mmHg		
Propofol	97 ± 9	86 ± 7*
SEVO pre	99 ± 8	91 ± 8*
SEVO post	98 ± 8	90 ± 7*
SEVO all	97 ± 7	96 ± 8†
dP/dt_{min}, mmHg/s		
Propofol	724 ± 69	619 ± 83*
SEVO pre	732 ± 78	653 ± 79*
SEVO post	717 ± 81	648 ± 68*
SEVO all	731 ± 73	711 ± 61†
ESP, mmHg		
Propofol	63 ± 4	54 ± 4*
SEVO pre	62 ± 3	57 ± 4*
SEVO post	61 ± 4	57 ± 3*
SEVO all	61 ± 3	60 ± 4†
τ, ms		
Propofol	58 ± 4	63 ± 3*
SEVO pre	59 ± 3	62 ± 2*
SEVO post	58 ± 3	61 ± 2*
SEVO all	57 ± 4	58 ± 4†

Data are presented as mean ± SD.

* Different between pre– and post–cardiopulmonary bypass (CPB) ($P < 0.05$). † Different from the propofol group ($P < 0.05$).

EDP = end-diastolic pressure; ESP = end-systolic pressure; LVP = left ventricular pressure; SEVO = sevoflurane; τ = time constant of isovolumic relaxation.

Table 4. Changes in LVP Data with Leg Elevation before and after CPB (n = 20/Group)

	Pre-CPB	Post-CPB
Δ EDP, mmHg		
Propofol	3 ± 2	7 ± 2*
SEVO pre	3 ± 1	6 ± 3*
SEVO post	3 ± 1	6 ± 2*
SEVO all	3 ± 2	4 ± 2†
Δ dP/dt_{max}, mmHg/s		
Propofol	33 ± 23	−49 ± 25*
SEVO pre	37 ± 27	−16 ± 19
SEVO post	34 ± 27	−12 ± 27
SEVO all	41 ± 26	41 ± 23†
Δ Peak LVP, mmHg		
Propofol	9 ± 3	3 ± 3*
SEVO pre	9 ± 2	5 ± 3*
SEVO post	9 ± 3	4 ± 3*
SEVO all	9 ± 3	8 ± 3†
Δ dP/dt_{min}, mmHg/s		
Propofol	73 ± 37	49 ± 52
SEVO pre	66 ± 29	51 ± 47
SEVO post	83 ± 43	63 ± 37
SEVO all	72 ± 35	59 ± 42
Δ ESP, mmHg		
Propofol	7 ± 2	5 ± 3
SEVO pre	7 ± 3	5 ± 2
SEVO post	7 ± 3	6 ± 2
SEVO all	8 ± 3	7 ± 3
Δ τ, ms		
Propofol	1 ± 3	5 ± 3*
SEVO pre	0 ± 3	3 ± 2*
SEVO post	1 ± 2	4 ± 2*
SEVO all	0 ± 2	1 ± 2†
R, ms/mmHg		
Propofol	0.41 ± 0.37	0.89 ± 0.43*
SEVO pre	0.39 ± 0.41	0.69 ± 0.32*
SEVO post	0.44 ± 0.39	0.73 ± 0.37*
SEVO all	0.35 ± 0.31	0.41 ± 0.39†

Data are presented as mean ± SD.

* Different between pre– and post–cardiopulmonary bypass (CPB) ($P < 0.05$). † Different from the propofol group ($P < 0.05$).

EDP = end-diastolic pressure; ESP = end-systolic pressure; LVP = left ventricular pressure; *R* = afterload dependency of left ventricular pressure decrease; SEVO = sevoflurane; τ = time constant of isovolumic relaxation.

SEVO post groups but not in the SEVO all group. Load dependence of LV pressure decrease (*R*) was similar in all groups before CPB. After CPB, *R* was increased in the propofol, SEVO pre, and SEVO post groups but remained unchanged in the SEVO all group.

The proportion of patients necessitating inotropic support with dobutamine was significantly ($P = 0.001$) related to the anesthetic regimen used (operating room: propofol group, n = 29; SEVO pre group, n = 17; SEVO post group, n = 20; SEVO all group, n = 10; intensive care unit: propofol group, n = 34; SEVO pre group, n = 20; SEVO post group, n = 25; SEVO all group, n = 14). Compared with the propofol group, the number of patients needing inotropic support was lower in the SEVO pre and the SEVO all group (operating room: propofol *vs.* SEVO pre, $P = 0.009$; propofol *vs.* SEVO post, $P = 0.10$; propofol *vs.* SEVO all, $P < 0.001$; intensive care unit: propofol *vs.* SEVO pre, $P = 0.03$; propofol *vs.* SEVO post, $P = 0.11$; propofol *vs.* SEVO all, $P < 0.001$). The need for vasoconstrictive therapy did not differ between the different anesthetic regimens used in this study design (operating room: propofol group, n = 15; SEVO pre group, n = 10; SEVO post group, n = 12; SEVO all group, n = 7; intensive care unit: propofol group, n = 20; SEVO pre group, n = 14; SEVO post group, n = 16; SEVO all group, n = 9).

Duration of stay in the intensive care unit and hospital duration of stay are displayed in figure 4. In the SEVO all group, the durations of stay in the intensive care unit and in the hospital were significantly lower than in the other groups. Because duration of stay in the intensive care unit may depend on factors other than strict medical indications, the number of patients who required a stay in the intensive care unit of longer than 48 h was also registered. The proportion of patients who required a stay of longer than 48 h was significantly ($P < 0.02$) related to the anesthetic regimen used (propofol group, n = 18; SEVO pre group, n = 14; SEVO post group, n = 12; SEVO all group, n = 5; propofol *vs.* SEVO pre, $P = 0.52$; propofol *vs.* SEVO post, $P = 0.28$; propofol *vs.* SEVO all, $P = 0.004$; SEVO all *vs.* SEVO pre, $P = 0.04$;

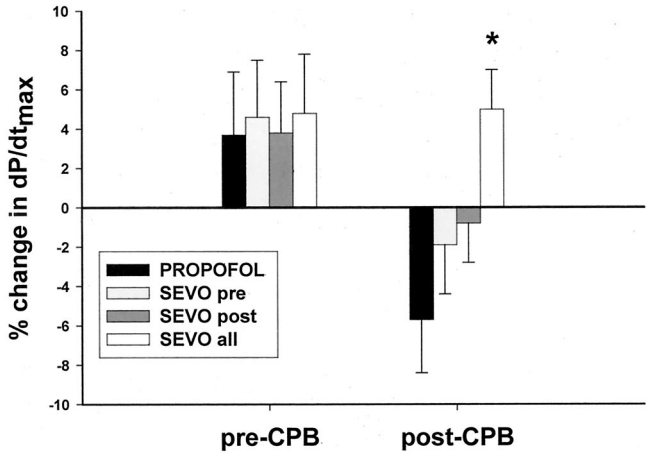

Fig. 3. Percentage change in maximal rate of pressure development (dP/dt_{max}) with leg elevation before (pre-CPB) and after cardiopulmonary bypass (post-CPB) with the different anesthetic protocols. Before CPB, the response to leg elevation was similar in the four groups. After CPB, leg elevation decreased dP/dt_{max} in all groups, except in the SEVO all group. Compared with pre-CPB, this different response was statistically significant in the propofol group but not in the SEVO pre group or the SEVO post group. Data are presented as mean ± SD. * Statistically significant difference with the propofol group ($P < 0.05$).

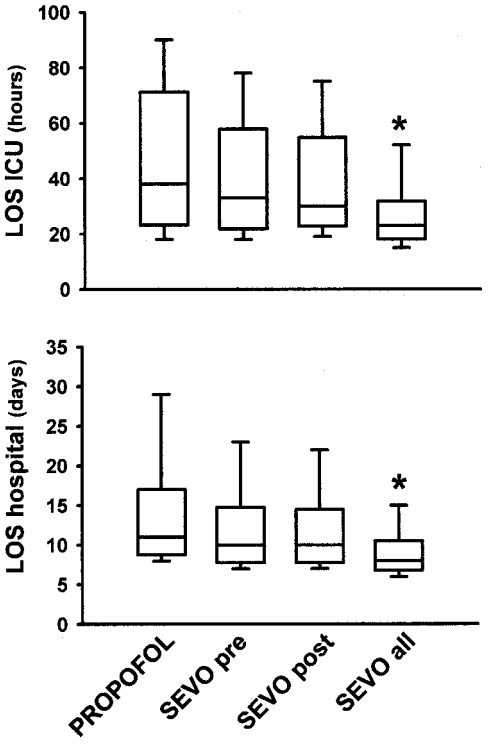

Fig. 4. Length of stay (LOS) in the intensive care unit (ICU) and in the hospital with the different anesthetic protocols used. Data are expressed as median with 25% and 75% confidence bars, and 5% and 95% confidence intervals. Compared with the propofol group, LOS was significantly lower in the SEVO all group. * Statistically significant difference with the propofol group ($P < 0.05$).

SEVO all *vs.* SEVO post, $P = 0.11$). Here also, it should be noted that the power of the performed statistical test for the comparisons between SEVO groups was below the desired power of 0.8. Therefore, the sample size was not sufficient to adequately address this issue, and the negative findings should be interpreted cautiously.

None of the patients included in the current study died in the hospital. A perioperative myocardial infarction developed in two patients (1%; one in the propofol group and one in the SEVO post group). Incidence of atrial fibrillation was not different among the four groups (six in the propofol group, four in the SEVO pre group, five in the SEVO post group, and two in the SEVO all group).

Discussion

The results of the current study indicated that the cardioprotective effects of an anesthetic regimen with sevoflurane were clinically most apparent when the volatile anesthetic was administered throughout the surgical procedure. This was evident from a lower postoperative troponin I release and a preservation of postoperative cardiac function when compared with a total intravenous anesthetic regimen. When administered only during the period before CPB, or only after completion of the coronary anastomoses, postoperative recovery of stroke volume occurred earlier, but the postoperative release of troponin I was not significantly different from the pattern observed with the intravenous anesthetic regimen.

Experimental observations have extensively shown that volatile anesthetic agents administered before and after ischemia improve cardiac function and reduce the occurrence of dysrhythmias on reperfusion.[1–11,27–31] These properties have been attributed to an anesthetic preconditioning effect,[1–6] but volatile agents may also have a protective action when administered only during the reperfusion period.[7–9]

In contrast to the experimental studies, the results from the clinical studies on the cardioprotective effects of anesthetic agents are less straightforward. These effects seem more important in protocols in which the volatile anesthetic was administered throughout the operative period.[17–20] Studies in which the volatile anesthetic was administered only before aortic clamping ("preconditioning" protocols) showed more variable results. Belhomme *et al.*[12] administered 2.5 minimum alveolar concentration (MAC) isoflurane for 5 min *via* the oxygenator of the CPB circuit followed by a 10-min washout period before aortic cross clamping. Isoflurane preconditioning (n = 10) resulted in an increased ectosolic activity of 5' nucleotidase (a surrogate marker for the activation of protein kinase C), but postoperative release of creatine kinase MB and troponin I was not different from that of the control group (n = 10). In a study of 22 patients, Penta de Peppo *et al.*[13] evaluated

the effects of 1.3% enflurane (range, 0.5–2%) administered through the respirator for 5 min immediately before CPB. In the study group, enflurane enhanced postoperative LV function, but postoperative creatine kinase MB and troponin I release were not different from the control group. In a study of 40 patients, Tomai *et al.*[14] administered 1.5% isoflurane for 15 min through the respirator followed by a washout period of 10 min before the start of CPB. No differences were observed between the treatment group and the control group in postoperative cardiac function and peak troponin I values. However, in the subgroup of patients with an LV ejection fraction less than 50%, troponin I concentrations 24 h postoperatively were lower in the isoflurane group (n = 9) than in the control group (n = 11). In another study of 49 patients, Haroun-Bizri *et al.*[15] administered 0.5–2% isoflurane until the start of CPB and observed a higher postoperative cardiac index in the isoflurane group than in the control group. To date, the largest study (72 patients) has been performed by Julier *et al.*[16] In this study, 4% sevoflurane was administered during the first 10 min of CPB just before aortic cross clamping. Compared with the control group, a significantly lower postoperative release of brain natriuretic peptide, a sensitive biochemical marker of myocardial contractile dysfunction, was observed. In addition, this study was the first to demonstrate that translocation of protein kinase C-δ and -ϵ isoforms—one of the mechanisms implicated as pivotal step in anesthetic preconditioning—also occurred in the human myocardium in response to sevoflurane. However, no differences were found between the groups for perioperative ST-segment changes, arrhythmias, creatine kinase MB, and cardiac troponin T release.

Clinical reports on the potential cardioprotective effects of volatile anesthetic agents when administered only during the reperfusion period are scarce. One unpublished study compared the effects of 1.5 MAC isoflurane administered on CPB during the first 15 min of reperfusion to a control group that received no isoflurane (Wolfgang Buhre, M.D., Ph.D., University of Aachen, Aachen, Germany, Ph.D. thesis, 2001). No differences were observed between groups in cardiac index, stroke volume index, and LV stroke work index, but a transient decrease in dP/dt_{min} was observed in the control group. Postoperative troponin T concentrations and lactate concentrations in coronary sinus blood were significantly lower in the isoflurane group.

The absence of an unequivocal and reproducible clinical protective effect on the different variables in these preconditioning and reperfusion protocols is in accord with the current results. Administration of sevoflurane only before CPB or only after completion of the coronary anastomoses was associated with minimal clinically apparent protective effects (earlier recovery of stroke volume in the immediate postoperative period [at T6 compared with T12 for the propofol group]). Therefore, it seems that the modalities of sevoflurane administration, such as timing and duration of exposure, may affect the degree of its cardioprotective properties.

The underlying mechanisms for this phenomenon remain to be established. Only a few studies have compared the magnitude of the cardioprotective effects of volatile anesthetics when administered only in the preconditioning or the reperfusion period. In a study on isolated guinea pig hearts, Varadarajan *et al.*[10] observed that sevoflurane administered both immediately before global myocardial ischemia and on reperfusion immediately after ischemia improved mechanical and metabolic function. In addition, both treatments were associated with a reduced Ca^{2+} loading on reperfusion. However, not only was sevoflurane administration before ischemia more protective than when administered on initial reperfusion, but there was also no additive protective effect when sevoflurane was administered before and after ischemia. The major effector of both preischemic and postischemic cardioprotective effect was the reduced Ca^{2+} loading, but combining the both protocols did not seem to result in enhanced protection against Ca^{2+} loading. These authors therefore suggested that sevoflurane initiates a maximal protective effect before ischemia that overrides the lesser protective effect of the agent on reperfusion. On the other hand, Obal *et al.*[11] observed in a study on anesthetized rats that myocardial protection with sevoflurane was further enhanced by sevoflurane administration during reperfusion. However, the cardioprotective effects by sevoflurane when administered during reperfusion were stronger than after its administration as a preconditioning stimulus.

Different causes have been implicated in the pathophysiology of myocardial reperfusion injury, including the interaction between polymorphonuclear neutrophils and the coronary endothelium.[32] Several experimental studies have demonstrated that volatile anesthetics may suppress neutrophil activation and the neutrophil–endothelium interaction and thereby preserve cardiac function.[33–35] Importantly, this protective effect was observed both in a "preconditioning" protocol[34] and in a "reperfusion" protocol.[35]

A possible explanation for the more pronounced effects in the SEVO all group is that the myocardial protection observed with volatile anesthetics is concentration dependent, with a more pronounced effect at higher concentrations, longer administration, or both. Several experimental studies have addressed this question. Kehl *et al.*[36] observed that low concentrations of isoflurane (0.25 or 0.5 MAC) were sufficient to precondition against myocardial infarction but that the efficacy of this treatment was diminished when coronary collateral blood flow was low. On the other hand, at higher concentrations of isoflurane (1.0 or 1.25 MAC), the cardioprotective effects were independent of the extent of collateral flow. Also, when administered in the reperfu-

sion period, the cardioprotective effects of sevoflurane were shown to be concentration dependent and time dependent. Obal *et al.*[9] demonstrated that administration of 1 MAC sevoflurane early during the reperfusion period reduced infarct size. A lower concentration of 0.75 MAC apparently had no effect on infarct size, whereas increasing the concentration of sevoflurane to 2 MAC had an effect on infarct size similar to that of 1 MAC. In another experimental study in rats, the same group observed that cardioprotection against reperfusion injury was maximal with only 2 min of sevoflurane administration and that a longer administration time resulted in lesser cardioprotective effects.[37] Although data obtained from experimental studies cannot unequivocally be transposed to a clinical setting of coronary surgery patients, they suggest that not only concentration but also duration and timing of the administration of the volatile anesthetic may be important in the extent of the cardioprotective effects.

In the current study, sevoflurane was titrated in the various groups according to hemodynamic and Bispectral Index values, necessitating concentrations ranging between 0.5 and 2%. This can imply that some differences may have occurred in the total concentrations of sevoflurane administered in the individual patients within each group. A potential more important confounding factor would have been a different duration of administration between patients in each group. However, duration of the different operative periods was similar in all patients (fig. 1 and table 1). On the other hand, the duration of sevoflurane administration was different according to the anesthetic protocol used. The patients in the SEVO all group received sevoflurane throughout the procedure, including the ischemic period on CPB. Therefore, it cannot be excluded that the better cardioprotective profile observed in the SEVO all group may, at least in part, be related to the longer administration of sevoflurane. Another possible explanation is that sevoflurane would have some beneficial effects during the ischemic period. A mechanism that has been proposed to account for the protection offered by volatile anesthetics during myocardial ischemia is the preservation of myocardial energy stores, allowing the myocardium to recover initially to a greater degree.[38] These effects have been attributed to a number of hemodynamic properties (decrease in afterload, contractility, and heart rate) that result in a lower myocardial energy demand and oxygen consumption, thereby reducing myocardial metabolic requirements. However, the ischemic period on CPB is characterized by the presence of a nonbeating, nonfibrillating heart that is completely empty. This implies that all hemodynamic variables responsible for myocardial oxygen consumption have been maximally reduced. In this particular setting, the negative inotropic and chronotropic properties of the volatile anesthetics therefore cannot be invoked as the sole reason for a better myocardial energy balance resulting in improved postoperative cardiac function.

Methodologic Issues

Several points deserve attention. First, the current protocols do not unequivocally allow attribution of the cardioprotective properties of sevoflurane to a preconditioning effect, a more favorable profile during the ischemic period, or an effect on reperfusion injury. Anesthetic preconditioning relates to a cardioprotective effect of an anesthetic that persists beyond the time of its administration. These cardioprotective effects were observed in experimental protocols in which the anesthetic agent was continued until the onset of myocardial ischemia but also in protocols where varying periods of anesthetic washout were allowed before ischemia was installed. This acute memory phase is a characteristic feature of preconditioning and seems to differ among anesthetics, with for example, a longer effect with isoflurane (> 30 min) than with sevoflurane (< 30 min).[4] To date, it is not definitively elucidated whether and how the washout modalities influence the cardioprotective mechanisms. Many characteristics of preconditioning by volatile anesthetics resemble those of ischemic preconditioning. It is not yet clear whether volatile anesthetics also elicit late preconditioning, but experimental data have indicated that volatile anesthetics may exert additive effects in combination with ischemic preconditioning.[4] These observations may have implications for the interpretation of the data from the current study. All patients underwent coronary surgery with CPB using intermittent aortic cross clamping. This may induce ischemic preconditioning, and as such, the better cardioprotective effects observed in the SEVO all group might be related to a combination of anesthetic and ischemic preconditioning effects. Another interesting point is the observation of Kevin *et al.*[39] that the protection of anesthetic preconditioning against contractile dysfunction and infarction (in an isolated guinea pig heart model) was restricted to a range of ischemia durations of 25–40 min and that prolonged ischemia was better tolerated by the coronary vasculature than by the myocardium. This may imply that the clinical applicability of anesthetic preconditioning as a cardioprotective tool in the treatment of patients with myocardial ischemia may depend on the duration of ischemia. If myocardial ischemia during coronary artery bypass surgery falls within the typical duration range, anesthetic preconditioning may provide a protective mechanism against cardiac dysfunction. However, if the duration of myocardial ischemia falls outside the range, this mechanism might provide no additional protection against reperfusion injury. Finally, a recent study in coronary surgery patients has reported that CPB as such was also able to trigger activation of the kinase cascade, indicating a potential preconditioning effect.[40] Administration of sevoflurane

on CPB during 10 min preceding aortic cross clamping did not increase kinase activation, nor did it improve markers of cell necrosis. These authors therefore suggested that the use of sevoflurane in such a protocol resulted in no additional beneficial effect compared with the effects of CPB. The current observations do not allow us to comment on potential preconditioning-like effects of CPB, but they confirm the previous observations[17,18] that the use of sevoflurane throughout the procedure of coronary surgery with CPB has cardioprotective effects.

The use of intermittent aortic cross clamping also implies that ischemic periods are repeatedly followed by periods of reperfusion. As such, reperfusion already occurs very early during the CPB period. Because the majority of alterations related to reperfusion injury occur rapidly within the first minutes of reperfusion, the beneficial effects in the SEVO all group might also be related to an effect on the extent of reperfusion injury during its administration on CPB.

The four different protocols used were part from a multidrug anesthetic regimen including a continuous infusion of remifentanil. Opioids may enhance the pharmacologic preconditioning effects of volatile agents.[41,42] However, remifentanil is a selective μ-opioid agonist, and cardioprotective effects of opioids have mainly been related to an activation of the δ-opioid receptor.[43] In addition, remifentanil was used in the same concentration range in all groups. All patients received corticoids, lidoflazine (a nucleoside transport inhibitor), and aprotinin. These interventions may have added to the cardioprotective effects observed. However, these regimens were uniformly applied in all patients in the different anesthetic protocols. In addition, all variables that might have contributed to differences in observations between groups were carefully controlled. Type of surgical procedure and distribution of surgical and cardioprotective technique were similar among all patients. Extent of coronary vascular disease, number of grafts, and duration of aortic cross clamping and CPB were also similar among all patients. Finally, preoperative data (including chronic preoperative medication, which could interfere with cardioprotective effects or affect outcome variables) were comparable among the four groups. Therefore, the only variable among the groups was the anesthetic protocol used, and possible differences between groups can be attributed to this variable.

Alternatively, the different recovery profiles between the SEVO all group and the propofol group could be explained not by a cardioprotective of the volatile anesthetic but by a detrimental effect of the dosages used of the particular intravenous agent. However, this is not likely to be the case. Transient myocardial dysfunction after coronary surgery with CPB is a well-known phenomenon[44–46] that has been observed with various anesthetic protocols. It is related to the ischemic burden associated with the surgical procedure and cannot be attributed to the use of a particular anesthetic drug regimen. Instead, it seems that the direct (irrespective of the favorable effects on the myocardial oxygen supply: demand ratio) cardioprotective effects of volatile anesthetics may offer an additional tool to protect the myocardium against the transient dysfunction associated with coronary surgery. This was recently confirmed in a study demonstrating that, compared with an intravenous anesthetic regimen with propofol or midazolam, the use of a volatile anesthetic regimen with sevoflurane or desflurane preserved myocardial function after CPB with a shorter intensive care unit duration of stay.[47]

In all groups, a number of patients required inotropic and vasoconstrictive support after CPB and in the first hours in the intensive care unit. It is obvious that this treatment influenced the analysis of cardiac function in the different groups. However, the need for inotropic support was significantly lower in the SEVO all group, which provided an additional indication that this anesthetic regimen resulted in better protection against myocardial dysfunction after CPB.

Sample size calculation was performed based on a difference in cardiac troponin I concentration at 24 h postoperatively of minimum 2 ng/ml between the different treatment groups. A significant difference in this primary outcome variable was observed only between the propofol group and the SEVO all group. The earlier recovery of stroke volume in the SEVO pre and the SEVO post groups compared with the propofol group suggests that these protocols may also result in some degree of cardioprotection. This was not evident from data on the primary outcome variable troponin I at 24 h postoperatively. However, it should be noted that the current study was not sufficiently powered to detect more subtle different responses in troponin I concentrations between groups. To demonstrate a difference in cardiac troponin I concentration at 24 h postoperatively of, for example, 1 ng/ml assuming a power of 0.8 and an α of 0.05, an estimated sample size of more than 300 patients in each group would be needed. This also implies that all published clinical "preconditioning" protocols are underpowered with respect to interpretation of the negative results on postoperative troponin concentrations.

In conclusion, the results of the current study indicated that in patients undergoing coronary artery surgery with CPB, the cardioprotective effects of an anesthetic regimen with sevoflurane were clinically most apparent when administered throughout the surgical procedure. When administered only before CPB or only after completion of the coronary anastomoses, postoperative recovery of stroke volume occurred earlier, but the postoperative troponin I release was not significantly different from the pattern observed with the intravenous anesthetic regimen.

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