Anesthesiology 2003; 99:314–23

Effects of Propofol, Desflurane, and Sevoflurane on Recovery of Myocardial Function after Coronary Surgery in Elderly High-risk Patients

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Background: **The present study investigated the effects of propofol, desflurane, and sevoflurane on recovery of myocardial function in high-risk coronary surgery patients. High-risk patients were defined as those older than 70 yr with three-vessel disease and an ejection fraction less than 50% with impaired length-dependent regulation of myocardial function.**

Methods: **Coronary surgery patients (n = 45) were randomly assigned to receive either target-controlled infusion of propofol or inhalational anesthesia with desflurane or sevoflurane. Cardiac function was assessed perioperatively and during 24 h postoperatively using a Swan-Ganz catheter. Perioperatively, a high-fidelity pressure catheter was positioned in the left and right atrium and ventricle. 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. Postoperative levels of cardiac troponin I were followed for 36 h.**

Results: **After CPB, cardiac index and dP/dt_{max} were significantly lower in patients under propofol anesthesia. Post-CPB, leg elevation resulted in a significantly greater decrease in dP/dt_{max} in the propofol group, whereas the responses in the desflurane and sevoflurane groups were comparable with the responses before CPB. After CPB, load dependence of left ventricular pressure drop was significantly higher in the propofol group than in the desflurane and sevoflurane group. Troponin I levels were significantly higher in the propofol group.**

Conclusions: **Sevoflurane and desflurane but not propofol preserved left ventricular function after CPB in high-risk coronary surgery patients with less evidence of myocardial damage postoperatively.**

MYOCARDIAL dysfunction after coronary bypass surgery is a well-known phenomenon that may significantly affect postoperative prognosis.[1–5] Not only the adequacy of the surgical revascularization but also the effectiveness of myocardial preservation will 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.[6–8]

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.[9] Volatile anesthetics have indeed been shown to directly precondition or indirectly enhance ischemic preconditioning, resulting in cardioprotection against myocardial infarction and irreversible myocardial dysfunction.[10–16] The implementation of this property during clinical anesthesia might provide an additional tool in the treatment and/or prevention of cardiac dysfunction in the perioperative period. Recently, several studies have reported evidence that volatile anesthetics have a beneficial effect on occurrence of myocardial dysfunction after coronary surgery. This effect was evident from a better cardiac performance and/or a reduced cardiac enzyme release in patients anesthetized with volatile anesthetics.[17–21]

Particularly in high-risk patients, the choice for an anesthetic regimen that preserves myocardial function may help to prevent postoperative cardiac dysfunction. To test this hypothesis, we analyzed recovery of ventricular function after coronary surgery in a group of high-risk patients in whom the only perioperative difference was the use of either propofol, desflurane, or sevoflurane in the anesthetic regimen. High-risk patients were defined as patients older than 70 yr, with three-vessel disease and an impaired myocardial function. The latter included the presence of a preoperative ejection fraction less than 50% and a deficient length-dependent regulation of myocardial function.[22–24] Baseline hemodynamic data, the ability of the left and right ventricle to sustain increased load,[22–24] and postoperative markers of myocardial tissue damage (cardiac troponin I) were compared in the three groups.

Methods

Patient Population

The study was approved by the Institutional Ethical Committee (University Hospital Antwerp, Edegem, Belgium) and written informed consent was obtained. The study was performed in coronary surgery patients older

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Received from the Department of Anesthesiology, University Hospital Antwerp, Edegem, Belgium. Submitted for publication November 8, 2002. Accepted for publication March 27, 2003. This research was supported by a government grant from the Fonds voor Wetenschappelijk Onderzoek (Onderzoekskrediet G.0.343.97, 1997-2000), Brussels, Belgium.

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than 70 yr with three-vessel disease and with a preoperative ejection fraction less than 50%. Patients undergoing repeat coronary surgery, concurrent valve repair, or aneurysm resection were excluded. Patients with unstable angina or with valve insufficiency were also excluded. Because antidiabetic agents from the sulfonylurea type and theophylline may interact with the mechanisms involved in the cardiac protective effects of preconditioning, 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 nadroparin 0.6 ml (5,700 U anti-Xa) subcutaneously. Patients were randomly (by opening of an envelope) allocated to receive either propofol (group A), desflurane (group B), or sevoflurane (group C) anesthesia. In the present study only patients with impaired length-dependent regulation of myocardial function[22–24] were included for analysis. These patients typically developed impairment of myocardial function with leg elevation, as manifested by the decrease in maximal rate of pressure development (dP/dt_{max}) and the increased load-dependence of rate of left ventricular pressure drop. A total of 45 patients (15 in each group) were included for analysis. All patients underwent coronary surgery using extracorporeal circulation.

Anesthesia and Surgery

All preoperative cardiac medication except for the angiotensin-converting enzyme inhibitors and the angiotensin II antagonists was continued until the morning of surgery. In the operating room patients received routine monitoring, including 5-lead electrocardiogram, radial and pulmonary artery catheters with continuous cardiac output measurement, pulse oxymetry, capnography, and blood and urine bladder temperature monitoring. In group A, anesthesia was induced with a continuous infusion of remifentanil at 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and a target-controlled infusion of propofol set at a target plasma concentration of 2 μg/ml. In group B, anesthesia was induced with diazepam 0.1 mg/kg combined with a continuous infusion of remifentanil at 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$. In group C, anesthesia was induced with a continuous infusion of remifentanil at 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$, sevoflurane was initially started at 8% and when the patient was asleep lowered to a concentration of 2%. In all groups muscle paralysis was obtained with pancuronium bromide 0.1 mg/kg. In group A, anesthesia was maintained with remifentanil 0.3–0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and target-controlled infusion of propofol set at a plasma target concentration of 2–4 μg/ml. In group B, anesthesia was maintained with remifentanil 0.3–0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and desflurane, 1–4%. In group C, anesthesia was maintained with remifentanil 0.3–0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and sevoflurane, 0.5–2%. 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 s throughout the cardiopulmonary bypass (CPB) period.

In each patient four sterilized, prezeroed electronic tip manometers (MTCP3Fc catheter, Dräger Medical Electronics, Best, The Netherlands; frequency response, 100 KHz) were inserted in both atria and ventricles. All 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-setting of the tip manometers were also checked against a high-fidelity pressure gauge (Druck Ltd., Leicester, UK) 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 left ventricular pressure tracings during an increase of systolic and diastolic pressures obtained by raising the caudal part of the surgical table by 45 degrees, thereby raising the legs. Leg elevation resulted in a rapid beat-to-beat increase in ventricular pressures.

A first set of measurements was obtained before CPB. After this measurement, the catheters were removed, the venous cannula 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 surgical technique for coronary artery bypass grafting, whereas the priming fluid of the CPB circuit contained 2.10^6 kallikrein-inhibiting units of aprotinin and 1 mg/kg lidoflazine. In addition, all patients had received 2 g methylprednisolone after induction of anesthesia.

During CPB, anesthesia was maintained in group A with remifentanil and target-controlled infusion propofol; in group B with remifentanil and desflurane; 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, the catheters were repositioned in the left and right atrium and 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 2.0 $l \cdot m^{-2} \cdot min^{-1}$, dobutamine was initiated. When mean arterial pressure was below 60 mmHg, vasoconstrictive therapy with phenylephrine was started. After a stabilization period of 15 min to allow for recovery of systolic and diastolic data after CPB, the post-CPB measurements were obtained.[25] Post-CPB, anesthesia was maintained with remifentanil combined with propofol in group A, desflurane 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 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 remifentanil 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and propofol at 2 mg/ml. Then 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 index (CI), and systemic vascular resistance index] were registered just before the start of surgery, before the start of CPB (pre-CPB), 15 min after the end of CPB (post-CPB), and at the end of the operation, 3 h after installation in the intensive care unit and 12 and 24 h later.

Atrial and ventricular 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 cardiac load and function were evaluated by the changes in EDP, peak ventricular pressure (left ventricular pressure and right ventricular pressure), ventricular pressure at dP/dt_{min} (= end-systolic pressure [ESP]), and dP/dt_{max}. Effects of leg elevation on rate of ventricular pressure drop 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 left ventricular 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 linearly fit 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 left ventricular pressure drop.[26,23] At least 10 consecutive beats were taken for the calculation of R. Sample correlation coefficients of the ESP–τ relationships yielded values of r greater than 0.92 in all patients. Analysis of cardiac performance data were completed in a blinded fashion with the person completing the analysis having no knowledge of the anesthetic regimen used in the patient.

Biochemical Analysis

Blood was sampled in all patients for determination of cardiac troponin I. These samples were obtained before the start of surgery (control) at arrival in the intensive care unit and at 3, 12, 24, and 36 h. 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.

Statistical Analysis

Sample size of the study was calculated based on cardiac troponin I level and the dP/dt_{max} post-CPB as primary outcome variable. For the cardiac troponin I level, a minimum detected difference of 2 ng/ml between the different treatment groups (propofol, desflurane, 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. For the dP/dt_{max} post-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 $\alpha = 0.05$, a sample size of 14 patients in each group was calculated to be appropriate.

Patients' characteristics were compared using Fisher exact test and a one-way ANOVA where appropriate. Medians were compared using the Kruskal-Wallis one-way ANOVA test on ranks. Hemodynamic data were tested for normal distribution. 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. Relations in hemodynamic parameters were analyzed using linear regression analysis computing Pearson's correlation coefficient. Slopes and intercepts of the relationships before and after CPB within each group were compared using *t* test analysis.[27] Because values of troponin I do not have a Gaussian distribution, the data were expressed as median and the 95% confidence interval. 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 (table 1). Complete revascularization was performed in all patients. One patient in the group A developed a myocardial infarction and died 24 h later. This patient was not included in the further analysis of hemodynamic and biochemical data. One patient in group B developed ventricular fibrillation after weaning from CPB, which was converted by defibrillation at 10 joules. This patient was also excluded from the study, leaving only 14 patients in this group. In addition, one patient in this group developed a transient atrial fibrillation in the first hours postoperatively, which returned spontaneously to sinus rhythm within the first 12 h. In all the other patients, hospital and intensive care unit stay were normal and recovery was uneventful.

Table 1. Patient Characteristics

	Propofol (n = 15)	Desflurane (n = 15)	Sevoflurane (n = 15)
Preoperative data			
Sex, M/F	13/2	13/2	13/2
Age, yr	76 ± 4	74 ± 3	75 ± 3
Length, cm	171 ± 9	171 ± 8	172 ± 7
Weight, kg	76 ± 12	80 ± 13	79 ± 12
BSA, m^2	1.88 ± 0.18	1.91 ± 0.18	1.90 ± 0.17
EF, %	43 ± 4	42 ± 5	39 ± 4
Previous myocardial infarction	6	6	7
Diabetes	3	5	4
COPD	2	2	3
Medication			
β-blockers	13	14	11
Calcium channel blockers	5	5	4
ACE inhibitors	5	7	6
Nitrates	12	10	10
Diuretics	5	5	5
Antiarrhythmic agents	0	0	0
Platelet aggregation inhibitors	13	13	11
Intraoperative data			
n° of bypasses	5 (3–6)	5 (3–6)	5 (3–6)
n° of arterial grafts	2 (1–3)	2 (1–3)	2 (1–3)
Cross-clamp time, min	47 ± 14	49 ± 7	46 ± 12
CPB time, min	102 ± 32	104 ± 33	100 ± 29

Data are mean (SD). n° of bypasses and arterial grafts are median (range).

ACE = angiotensin-converting enzyme; BSA = body surface area; COPD = chronic obstructive pulmonary disease; CPB = cardiopulmonary bypass; EF = ejection fraction.

Mean arterial pressure, mean pulmonary artery pressure, central venous pressure, and systemic vascular resistance index were kept stable throughout in all groups. Post-CPB and at the end of the operation and at 3 h, CI was decreased in group A but not in groups B and C (table 2). From 12 h on, the transient decrease in CI in group A had normalized. Post-CPB, the need for inotropic support was significantly higher in group A (10 patients *vs.* 4 patients in group B and 3 in group C). The need for vasoconstrictive therapy was similar in all groups (6 patients in group A, 5 in group B, and 4 in group C). In the intensive care unit, the need for inotropic support was significantly higher in group A (12 patients *vs.* 5 patients in group B and 4 in group C). The

Table 2. Pre- and Postoperative Hemodynamic Data

	Base	Pre-CPB	Post-CPB	End	ICU T3	ICU T12	ICU T24
MAP (mmHg)							
Propofol (n = 14)	76 ± 10	74 ± 9	72 ± 5	73 ± 6	79 ± 15	77 ± 13	78 ± 14
Desflurane (n = 14)	76 ± 6	73 ± 7	76 ± 6	78 ± 12	84 ± 12	83 ± 12	82 ± 8
Sevoflurane (n = 15)	74 ± 11	71 ± 9	74 ± 6	76 ± 6	86 ± 13	82 ± 7	83 ± 7
MAP (mmHg)							
Propofol	23 ± 3	22 ± 2	24 ± 2	24 ± 2	22 ± 4	20 ± 5	20 ± 5
Desflurane	23 ± 3	24 ± 2	24 ± 3	24 ± 3	23 ± 3	18 ± 3	19 ± 3
Sevoflurane	22 ± 3	22 ± 3	23 ± 3	24 ± 2	21 ± 3	21 ± 3	20 ± 3
CVP (mmHg)							
Propofol	12 ± 2	11 ± 2	13 ± 2	13 ± 2	12 ± 3	10 ± 3	10 ± 3
Desflurane	13 ± 3	13 ± 3	14 ± 3	13 ± 3	12 ± 3	9 ± 3	9 ± 3
Sevoflurane	10 ± 2	12 ± 2	12 ± 2	12 ± 2	10 ± 2	10 ± 3	9 ± 2
CI ($l \cdot min \cdot m^{-2}$)							
Propofol	2.4 ± 0.5	2.3 ± 0.5	2.0 ± 0.4†	2.1 ± 0.3†	2.3 ± 0.4†	2.4 ± 0.5	2.6 ± 0.5
Desflurane	2.3 ± 0.5	2.5 ± 0.7	2.5 ± 0.5	2.6 ± 0.2	2.6 ± 0.4	2.6 ± 0.6	2.8 ± 0.5
Sevoflurane	2.3 ± 0.5	2.4 ± 0.4	2.7 ± 0.3	2.8 ± 0.3	2.8 ± 0.4	2.7 ± 0.6	2.8 ± 0.4
SVRI ($dyne \cdot s \cdot cm^{-5} \cdot m^{-2}$)							
Propofol	1,795 ± 498	1,889 ± 439	1,932 ± 356	1,856 ± 261	1,760 ± 541	1,736 ± 396	1,826 ± 432
Desflurane	1,785 ± 339	1,772 ± 278	1,789 ± 345	1,833 ± 500	1,897 ± 438	1,768 ± 295	1,765 ± 193
Sevoflurane	1,822 ± 456	1,859 ± 369	1,731 ± 216	1,735 ± 245	1,846 ± 380	1,725 ± 245	1,746 ± 291

* Different compared with base; † different compared with other groups.

CI = cardiac index; CVP = central venous pressure; MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; SVRI = systemic vascular resistance index.

Table 3. Left and Right Ventricular Pressure Data before and after CPB

	pre-CPB	post-CPB
LVEDP, mmHg		
Propofol (n = 14)	12 ± 4	16 ± 5*
Desflurane (n = 14)	11 ± 4	14 ± 4*
Sevoflurane (n = 15)	11 ± 4	14 ± 3*
RVEDP, mmHg		
Propofol	12 ± 4	12 ± 4
Desflurane	11 ± 3	12 ± 3
Sevoflurane	12 ± 2	11 ± 4
LV dP/dt_{max}, mmHg/s		
Propofol	799 ± 68	645 ± 72*†
Desflurane	816 ± 78	802 ± 77
Sevoflurane	821 ± 64	823 ± 82
RV dP/dt_{max}, mmHg/s		
Propofol	198 ± 81	190 ± 81
Desflurane	180 ± 76	194 ± 43
Sevoflurane	184 ± 46	197 ± 45
Peak LVP, mmHg		
Propofol	90 ± 10	82 ± 7*†
Desflurane	90 ± 10	89 ± 8
Sevoflurane	89 ± 9	89 ± 9
Peak RVP, mmHg		
Propofol	33 ± 9	34 ± 5
Desflurane	34 ± 10	37 ± 5
Sevoflurane	32 ± 7	34 ± 5
LVESP, mmHg		
Propofol	55 ± 5	47 ± 5*†
Desflurane	53 ± 5	52 ± 6
Sevoflurane	53 ± 4	53 ± 5
LV ejection time, ms		
Propofol	362 ± 25	328 ± 19*†
Desflurane	361 ± 18	342 ± 30*
Sevoflurane	364 ± 29	343 ± 19*
LV τ, ms		
Propofol	67 ± 4	75 ± 3*†
Desflurane	68 ± 6	67 ± 4
Sevoflurane	68 ± 5	68 ± 3

Data are mean ± SD.

*Different between pre- and post-CPB. † Different from other groups.

CPB = cardiopulmonary bypass; LV = left ventricle; LVEDP = left ventricular end-diastolic pressure; LVESP = left ventricular end-systolic pressure; τ = time constant of relaxation; RV = right ventricle; RVEDP = right ventricular end-diastolic pressure.

Table 4. Changes in Left and Right Ventricular Pressure Data with Leg Elevation before and after CPB

	pre-CPB	post-CPB
ΔLVEDP, mmHg		
Propofol (n = 14)	8 ± 2	12 ± 2*†
Desflurane (n = 14)	7 ± 2	6 ± 2
Sevoflurane (n = 15)	8 ± 2	6 ± 3
ΔRVEDP, mmHg		
Propofol	6 ± 2	6 ± 2
Desflurane	7 ± 2	6 ± 2
Sevoflurane	6 ± 2	6 ± 1
Δ LV dP/dt_{max}, mmHg/s		
Propofol	−50 ± 11	−138 ± 18*†
Desflurane	−55 ± 12	−57 ± 11
Sevoflurane	−57 ± 14	−49 ± 12
Δ RV dP/dt_{max}, mmHg/s		
Propofol	14 ± 13	8 ± 14
Desflurane	7 ± 14	−5 ± 13
Sevoflurane	24 ± 16	15 ± 11
Δpeak LVP, mmHg		
Propofol	10 ± 4	5 ± 3*†
Desflurane	11 ± 3	9 ± 4
Sevoflurane	10 ± 3	10 ± 4
ΔLV ejection time, ms		
Propofol	15 ± 11	1 ± 6*
Desflurane	15 ± 10	13 ± 9
Sevoflurane	16 ± 7	13 ± 7
Δ LV τ, ms		
Propofol	4 ± 2	8 ± 2*†
Desflurane	5 ± 1	4 ± 2
Sevoflurane	5 ± 2	4 ± 2
R, mmHg/s		
Propofol	0.77 ± 0.21	1.58 ± 0.12*†
Desflurane	0.76 ± 0.15	0.81 ± 0.11
Sevoflurane	0.78 ± 0.15	0.79 ± 0.11

Data are mean ± SD.

* Different between pre- and post CPB. † Different from other groups.

CPB = cardiopulmonary bypass; LV = left ventricle; LVEDP = left ventricular end-diastolic pressure; π = time constant of relaxation; R = afterload dependence of LV pressure drop; RV = right ventricle; RVEDP = right ventricular end-diastolic pressure.

need for vasoconstrictive therapy in the intensive care unit was similar in the three groups (5 patients in group A, 5 in group B, and 4 in group C).

Left ventricular end-diastolic pressure was increased after CPB in all groups. Left ventricular dP/dt_{max} decreased post-CPB in group A but not in groups B and C ($P < 0.05$). Peak left ventricular pressure and ESP decreased post-CPB in group A but not in the groups B and C. Post-CPB, the time constant of isovolumic relaxation (τ) was increased in group A but not in groups B and C (table 3). RV pressure and pressure-derived data were not significantly altered after CPB in the present study population.

Leg elevation increased EDP. The increase in EDP was higher post-CPB than pre-CPB in group A but not in groups B and C (table 4). Before CPB, the decrease in dP/dt_{max} with leg elevation was similar in all groups (−6 ± 3% in group A, −7 ± 3% in group B, and −7 ± 3% in group B). Post-CPB, the decrease in dP/dt_{max} with leg elevation was significantly more pronounced in group A ($P < 0.05$) (−19 ± 3% in group A, −6 ± 2% in group B, and −5 ± 2% in group C) (fig. 1). Peak left ventricular pressure increased similarly with leg elevation in all groups before CPB. After CPB, the increase in left ventricular pressure with leg elevation was less than before CPB in group A. 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 diastole to dP/dt_{min} with leg elevation was similar before and after CPB in the groups B and C but not in group A. After CPB, the increase in τ with leg elevation was significantly higher in group A. Load dependence of left ventricular pressure drop (R) was similar in all groups before CPB. After CPB, R increased significantly in group A but not in groups B and C. The effects of leg elevation on right ventricular performance were similar before and after CPB in the different study groups.

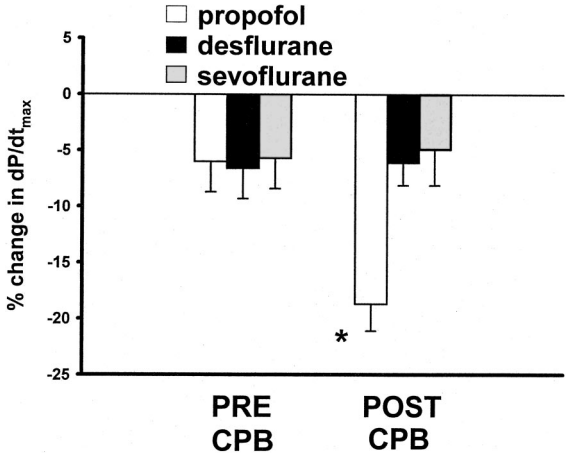

Fig. 1. Percentage change in maximal rate of pressure development (dP/dt_{max}) with leg elevation before and after cardiopulmonary bypass (CPB) with the different anesthetic regimens. With desflurane and sevoflurane the response to leg elevation is similar before and after CPB. With propofol, the decrease in dP/dt_{max} is significantly more pronounced after CPB.

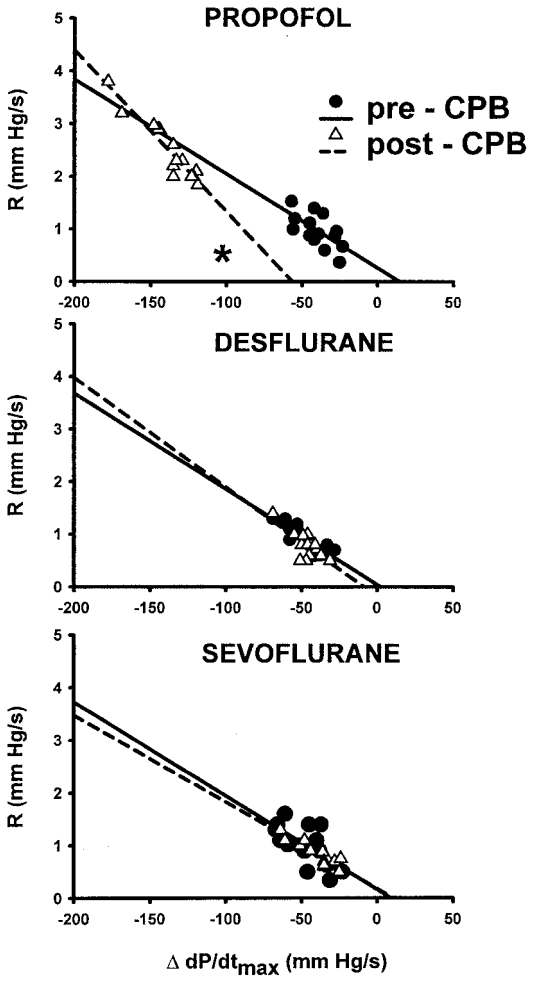

Fig. 2. Plots relating individual values of R (load dependence of left ventricle pressure drop) to corresponding changes in dP/dt_{max} with leg elevation. On each plot, the data before (*filled circles*) are compared with the data after (*open triangles*) cardiopulmonary bypass (CPB). For desflurane and sevoflurane, the relationships are similar before and after CPB. With propofol both intercept as slope have changed after CPB. For the sake of clarity, the 95% confidence lines have not been drawn. * slope and intercept significantly different from pre-CPB.

Variables of contraction ($\Delta dP/dt_{max}$) and relaxation (R) were coupled. A close relationship was found between changes in dP/dt_{max} and individual values of R in all experimental conditions (fig. 2). Before CPB, the relationship between changes in dP/dt_{max} and individual values of R were comparable in the three groups (group A: $y = 0.194 - (0.018^*x)$, $r = 0.75$, $P < 0.001$; group B: $y = 0.08 - (0.018^*x)$, $r = 0.86$, $P < 0.001$; group C: $y = 0.166 - (0.018^*x)$, $r = 0.79$, $P < 0.001$). After CPB, the relationship between changes in dP/dt_{max} and individual values of R were not altered in groups B and C, but in group A both slope and intercept differed significantly from before CPB (group A: $y = -1.718 - (0.031^*x$, $r = 0.85$, $P < 0.001$; group B: $y = -0.181 - (0.021^*x)$, $r = 0.74$, $P < 0.001$; group C: $y = 0.179 - (0.017^*x)$, $r = 0.88$, $P < 0.001$).

Figure 3 illustrates the evolution of the cardiac troponin I levels during the first 36 h postoperatively. Troponin I levels increased in all patients throughout the observation period. From 3 h on, troponin I levels were significantly higher in group A than in groups B and C. In group A, 13 of the 14 patients showed an increase of troponin I levels above the cutoff value of 2 ng/ml, whereas this was the case in only 5 patients in group B and 4 patients in group C.

Discussion

Transient myocardial dysfunction after coronary bypass surgery is a well-recognized phenomenon.[1–5] Not only the adequacy of the surgical revascularization but also the effectiveness of myocardial preservation determines the maintenance of ventricular function and the postoperative outcome. The results of the present study indicated that, in addition to these different factors, the choice of the anesthetic regimen also influences postoperative myocardial function and extent of myocardial damage in high-risk coronary surgery patients. Indeed, the patients who were anesthetized with sevoflurane and desflurane had significantly better function, lower postoperative troponin I levels, and less need for inotropic support than the patients anesthetized with propofol.

Patients' characteristics were similar in the three groups. Pre- and perioperative anticoagulation therapy was similar and all patients had a complete revascularization. The number of grafts, type of cardioprotection, duration of aortic cross-clamp time, and CPB were also similar in all patients, which suggests that the differences in cardiac function between the groups were not caused by differences in patients' characteristics and intraoperative events but instead seem to be related to the choice of anesthetic agent.

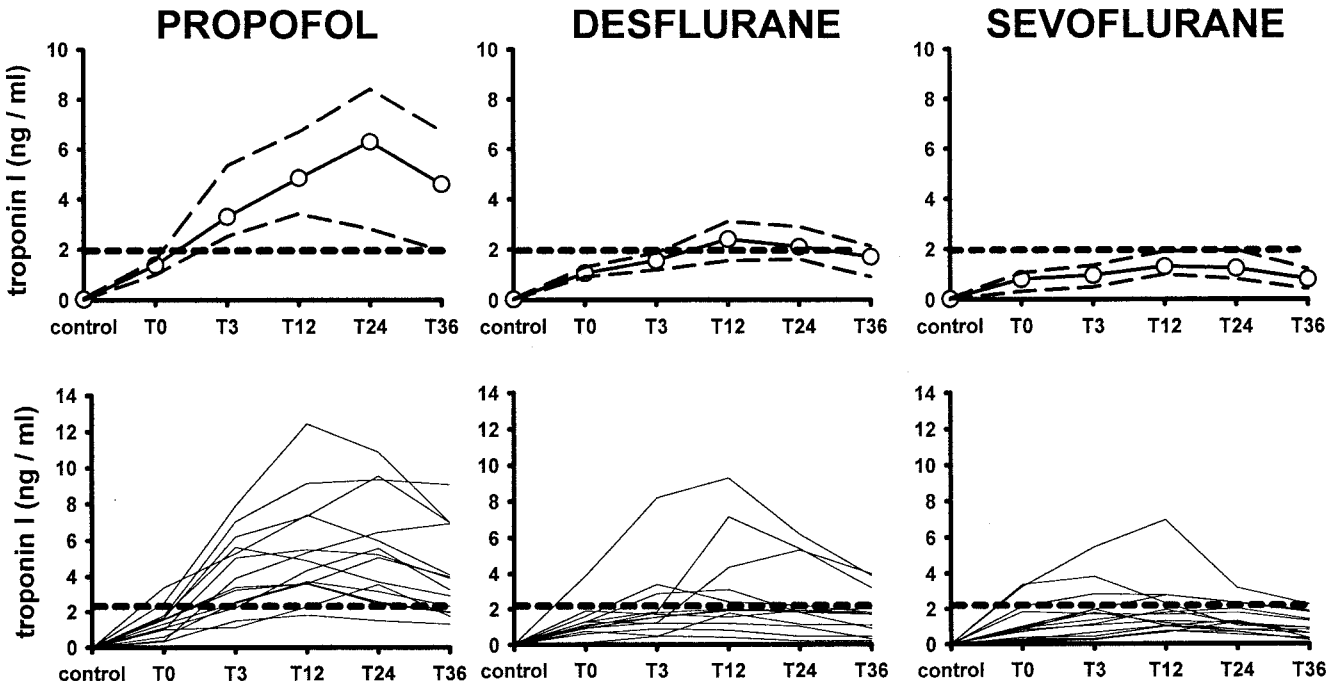

Fig. 3. Cardiac troponin I concentrations in the three groups before surgery (control), at arrival in the intensive care unit (T0), and after 3 (T3), 12 (T12), 24 (T24), and 36 (T36) h. The *upper panels* show the median values with 95% confidence intervals. The *lower panels* show the evolution of the individual values. Concentrations were significantly higher with propofol anesthesia.

The underlying mechanisms responsible for the differences in postoperative cardiac function and extent of myocardial damage in these patients cannot be elucidated from the present study. It is impossible in the presence of an unknown and unquantified decrement in cardiac function related to the 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.[9–15] Whereas the available data on volatile anesthetics seem rather straightforward, the data on possible cardioprotective effects of propofol seem more controversial. Volatile anesthetics have indeed been shown to directly precondition or indirectly enhance ischemic preconditioning, resulting in cardioprotection against myocardial infarction and irreversible myocardial dysfunction.[10–16] Propofol, on the other hand may enhance the antioxidant capacity, and this property has been claimed to protect the myocardium.[28–30] The possible implications of this increase in antioxidant capacity for preservation of tissue function, however, remain to be demonstrated. Ko *et al.*[31] reported that propofol at higher concentrations (100 μM) attenuated mechanical, biochemical, and histologic changes caused by myocardial ischemia and reperfusion, but Ebel *et al.*[32] found no protective effect against myocardial reperfusion injury of propofol at clinically relevant concentrations. Similarly, Coetzee reported that propofol provided no functional benefit in reperfused pig myocardium.[33] In a recent publication, Ansley *et al.*[34] observed that high-dose propofol (2–2.5 mg/kg bolus followed by a continuous infusion of 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$) enhanced red blood cell antioxidant capacity during CPB in humans. Red blood cell antioxidant capacity with low-dose propofol or isoflurane anesthesia was on the contrary similar. The authors related this increased antioxidant capacity in the high-dose propofol group to improved myocardial function (higher cardiac index) 12 h postoperatively. In the current study, propofol was administered using a target-controlled infusion system that was set to obtain a target plasma propofol concentration of 2–4 μg/ml. This plasma concentration is far beyond the concentrations at which cardioprotective effects have been described.[31,34] With respect to the potential role of free radicals in the occurrence of myocardial dysfunction, it is of interest to note that recent work has suggested that suppressing the formation of reactive oxygen species in the heart may actually be detrimental. In a study on rabbits, Müllenheim *et al.*[35] demonstrated that the release of free radicals is crucially involved in mediating the cardioprotective effects of isoflurane-induced preconditioning and that administration of free-radical scavengers abolish the cardioprotective effects of isoflurane. An alternative explanation for the failure of propofol to preserve the myocardial function at clinically relevant concentrations might exactly be its property to scavenge the free radicals, necessary to trigger the preconditioning effects.

Interestingly, several experimental studies have reported that aging is associated with the loss of ischemic preconditioning.[36–39] It is unclear to what extent this phenomenon is also present in the experimental settings of anesthetic preconditioning. Although the present observations demonstrated maintenance of cardiac function after coronary surgery with CPB in elderly patients, the methodology of our study does not allow us to comment on this issue. Clearly, further research is necessary to unravel the exact underlying mechanisms of the possible myocardial effects of the different anesthetic regimes.

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 complete recovery within 4 h, whereas an ejection fraction less than 45% was associated with more severe dysfunction and a longer period of recovery.[4] Yet ejection fraction as an index of ventricular performance is highly afterload-dependent.[40] Therefore, its usefulness as a sole measure of ventricular function is limited. Indeed, the baseline preoperative ejection fraction will not necessarily inform on the heart's capacity to deal with an additional stress placed on the system. It has been reported previously that the response to an increase in cardiac load is variable in coronary surgery patients. Some patients show an improvement of myocardial function with an increase in stroke area and dP/dt_{max} and an acceleration of left ventricular pressure drop, whereas in other patients either no change or even an impairment of myocardial function occurs. These patients typically develop a decrease in stroke area and dP/dt_{max}, an enhanced load-dependence of left ventricular pressure drop, and a marked increase in left ventricular EDP. Patients with this type of response pre-CPB seem to necessitate more often inotropic support with dobutamine to be successfully weaned from CPB.[22] In the present study, patients with the latter type of response were selected. This allowed us to study 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. Recent *in vitro* evidence has indicated that ischemic preconditioning cannot be elicited in tissue of failing human hearts with an ejection fraction less than 30%.[41] Because one of the possible explanations for the observed differences between the anesthetic regimens might be related to the preconditioning effects of volatile agents, it would be interesting to study whether similar results can be obtained in patients with more severe heart failure.

A number of methodologic issues should be taken into account with respect to the present observations. Propofol, desflurane, and sevoflurane were used as part of a multidrug anesthetic regimen. Opioids were shown to mimic the cardioprotective effect of ischemic preconditioning.[42] 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, desflurane, and sevoflurane. Another difference between the groups is the use of diazepam during induction of anesthesia in the desflurane group. In this study, we aimed to limit the number of drugs used to clearly relate possible different effects to the anesthetics used. For groups A and C, both induction as maintenance of anesthesia could be obtained with the same drug. However, induction of anesthesia with desflurane is not possible. For this reason, induction of anesthesia in the patients of group B was obtained with diazepam. It cannot be excluded that this may have contributed to the effects observed in group B. Effects of intravenous anesthetics on preservation of myocardial function are subject of ongoing research. Recently, it was shown that the benzodiazepine midazolam had no effect on mitochondrial K_{ATP} channel activity in isolated adult rat cardiomyocytes, suggesting that no additional cardioprotection was to be expected with this type of drug.[43]

In all groups, a number of patients needed inotropic and vasoconstrictive support after CPB and in the first hours in the intensive care unit. Obviously this treatment has influenced the analysis of cardiac function in the different groups. The current data may therefore not be interpreted as net effects of propofol, desflurane, 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 desflurane and sevoflurane better protected against myocardial dysfunction after CPB.

Cardiac troponin I is a sensitive marker for myocardial cellular damage.[44,45] Postoperative values of these enzymes were significantly lower in the desflurane 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 and clearly above the cutoff value of 2 ng/ml and comparable to the value of 5.2 μg/l reported by Sadony[46] in patients classified as having minor myocardial damage. Still, they compare favorable with the cutoff value of 13.4 μg/l reported by Jacquet[47] to significantly separate patients with an uneventful recovery from those with myocardial ischemia and infarction. The levels of troponin I observed in the

propofol and sevoflurane groups are comparable with those that were previously observed in coronary surgery patients with good preoperative ejection fractions.[19] This 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.

In the present study, postoperative troponin I levels and post-CPB myocardial function were used as outcome variables. Obviously, this represents only part of the clinical spectrum. Other outcome variables such as the occurrence of rhythm disturbances, perioperative morbidity and mortality, and others are also important to assess. To address these issues, large multicenter trials should now be designed and performed.

It should be noted that in the present study right ventricular pressure data and pressure-derived data—in contrast to the left ventricular data—were not altered by CPB. The right ventricle functions as a low-pressure volume pump, whereas the left ventricle is essentially a pressure pump.[48] This implies that changes in right ventricular function will primarily be reflected in the volume data and not in the pressure data. CI, which is measured at the level of the right ventricle, also showed a transient decrease of function in the propofol group and not with the volatile anesthetics. This indicated that the protective effects of desflurane and sevoflurane occurred for the function of both the left and right ventricles.

In conclusion, in high-risk coronary surgery patients with documented impairment of myocardial function, anesthesia with desflurane and sevoflurane preserved cardiac function after CPB with less evidence for myocardial damage than with propofol. This also indicated that in high-risk patients, in whom any additional perioperative myocardial ischemic injury can severely affect postoperative function and outcome, the choice of the anesthetic regimen might help to preserve cardiac function after coronary surgery.

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